UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: June 21, 2012

Subject: Paraquat Dichloride. Human Health Risk Assessment for the Request to Add Uses on Perennial Tropical and Sub-Tropical Fruit Trees.

PC Code: 061601	**DP Barcode:** D399869
Decision No.: 437241	**Registration No.:** None
Petition No.: 0E7748	**Regulatory Action:** Section 3 Registration
Risk Assessment Type: NA	**Case No.:** 0262
TXR No.: NA	**CAS No.:** 1910-42-5
MRID No.: None	**40 CFR:** 180.205

From: Thurston G. Morton, Chemist
Jessica Ryman, Ph.D., D.A.B.T., Toxicologist
Ayaad Assaad, Toxicologist
James S. Miller, Environmental Scientist
Risk Assessment Branch IV
Health Effects Division (7509P)

Susan V. Hummel
for

Through: Susan V. Hummel, Senior Chemist
Elissa Reaves PhD., Branch Chief
Risk Assessment Branch IV
Health Effects Division (7509P)

To: Andrew Ertman
Barbara Madden
Risk Integration, Minor Use & Emergency Response Branch
Registration Division (RD) (7505P)

This document provides the Health Effects Division's (HED's) risk assessment of the new proposed use on Perennial Tropical and Sub-Tropical Fruit Trees.

1.0 EXECUTIVE SUMMARY

Syngenta Crop Protection, in PP#0E7748, has proposed the establishment of tolerances for residues of the herbicide paraquat (1,1'-dimethyl-4,4'-bibyridinium ion) derived from the application of the dichloride salt (calculated as the cation) to perennial tropical and sub-tropical fruit trees.

Use Profile

Paraquat dichloride (hereafter in this document referred to solely as paraquat) is a non-selective herbicide currently registered for the control of weeds and grasses in agricultural and non-agricultural areas, and for use as a defoliant, desiccant, and plant growth regulator. The Paraquat Reregistration Eligibility Decision (RED) Document (EPA 738-F-96-018) was issued in August 1997. The Product and Residue Chemistry Chapters of the RED were completed in July of 1995 (D217262, D. Miller). Currently all registered end-use products are formulated as paraquat dichloride, and the active ingredient is expressed in terms of the paraquat cation.

Tolerances for residues of paraquat have been established under 40CFR§180.205. The tolerances are expressed in terms of residues of paraquat derived from application of either the bis(methyl sulfate) or the dichloride salt (both calculated as the cation). Because there are currently no registered products containing paraquat dimethyl sulfate, the tolerance expression listed under 40CFR§180.205(a) and §180.205(c) should be revised to remove reference to the bis(methyl sulfate) salt of paraquat.

General tolerances have been established under 40CFR§180.205(a), and range from 0.01 ppm for egg and milk to 210 ppm for Animal feed, nongrass, group 18, hay. Tolerances with regional registration have been established under 40CFR§180.205(c) at 0.05 ppm for cassava, pigeon pea seed, tanier, tyfon, and true yam, and at 0.1 ppm for taro corm.

The RED Document (EPA 738-F-96-018, 8/97) recommended numerous changes to paraquat tolerances. A Federal Register notice proposing these changes was published on 8/4/2004 (69 FR 47051-47068). The proposed tolerance revisions have not as yet been finalized.

Proposed New Uses

IR-4 has submitted copies of the registered label for a 2.0 lb paraquat cation/gal soluble concentrate (SC) formulation of paraquat dichloride (Gramoxone Inteon; EPA Reg. No. 100-1217). Gramoxone Inteon is proposed for postemergence directed spray to the floor of orchards of perennial tropical and sub-tropical fruit trees. Maximum application rate is 0.94 lb a.i./A. A maximum of four applications is proposed along with a 14-day pre-harvest interval (PHI).

Hazard Identification

The toxicology database for paraquat is considered complete. The primary target organ of paraquat is the lung. Evidence of lung inflammation, scarring, and compromised lung function in response to paraquat are observed throughout the toxicity database in different species (rats, mice, and dogs). Effects in the respiratory tract are observed after acute, subchronic, and chronic exposures regardless of the route of exposure (oral or inhalation). However, inhalation was a more sensitive route of exposure than the oral route. With increasing durations of exposure, effects of paraquat in other organ systems are observed. These effects include liver inflammation and necrosis in rats and inflammation and necrosis of the kidneys in rats and mice. Lenticular changes in the eyes of rats were also observed with increasing durations of exposure. Importantly, the lung effects occur at doses lower than effects in these other organs systems, and so protecting for lung effects protects for all other adverse effects of paraquat.

The effects of paraquat in lungs are considered systemic effects. There are no dermal toxicity studies suitable for evaluation of systemic lung effects in the toxicity database for paraquat. Therefore, the Agency is using a dermal absorption factor of 0.3%, which was derived from dermal absorption studies conducted in humans and monkeys and an oral endpoint for dermal risk assessments.

Paraquat does not cause reproductive toxicity. Developmental toxicity in response to parquat, when observed, always occurred in the presence of maternal toxicity. Four developmental toxicity studies (two in rats and two in mice) are available. If developmental toxicity was present, clear no adverse effect levels were identified which were equivalent to (or exceeded) those for maternal toxicity. Therefore, there was no evidence of quantitative susceptibility. The kinds of developmental effects observed (e.g. reduced body weight/gain and delayed skeletal ossification) are effects that commonly observed secondary to maternal toxicity. These developmental effects, when present, differed in nature but were considered of lesser severity than those observed in maternal animals (e.g. respiratory distress, reduced body weight, lesions in the lungs and kidneys). Since effects in the offspring, when present, were lesser in severity than those observed in maternal animals and were also consistent with those commonly observed as secondary to maternal toxicity, the Agency has concluded that there was no evidence of qualitative susceptibility in the young.

Previously, the Agency had required that a developmental toxicity study in rabbits be conducted for paraquat. As a result, the FQPA Safety Factor had been retained as a 3X database uncertainty factor for Females 13-39 for the acute dietary risk assessment only. The Agency recently reviewed the toxicity database for paraquat and concluded that a developmental toxicity study in rabbits was not likely to add information that would impact the paraquat risk assessment. Therefore, this study is no longer required and the FQPA Safety Factor has been reduced to 1X for this population.
No evidence of neurotoxicity was observed in acute and subchronic neurotoxicity studies conducted with paraquat up to the doses at which respiratory effects were observed (e.g. the maximum tolerated dose). There was also no evidence of immunotoxicity in response to paraquat.

Paraquat was found to be weakly positive in the mouse lymphoma assay and human lymphocyte cytogenetic assay, and was positive in the sister chromatid exchange assay. Conversely, paraquat was not mutagenic in the *Salmonella typhimurium* assay, was not genotoxic in the unscheduled DNA synthesis assay *in vitro* or *in vivo*, was negative for chromosomal aberration in the bone marrow test, and no evidence was found for suppressed fertility or dominant lethal mutagenicity in mice. The Cancer Peer Review Committee and the Science Advisory Committee (1989) concluded that there was no evidence of carcinogenicity in animal studies and classified paraquat as a Group E chemical (evidence of non-carcinogenicity in humans).

Paraquat is severely toxic following acute exposure via the dermal and inhalation routes (Category I) and only slightly less toxic by the oral route of exposure (Category II). It is a dermal and ocular irritant but is not a skin sensitizer.

Dose Response Assessment

Toxicological points of departure (PODs) were selected for dietary/drinking water and occupational exposure scenarios for this assessment. Acute and chronic reference doses (RfDs) were selected for assessment of food and drinking water exposures. The population adjusted dose (PAD) is equivalent to the reference dose (RfD) divided by the additional FQPA Safety Factor, which was reduced to 1X for All Populations. An acute RfD/PAD for all populations was selected from a multi-generation study in rats which showed increased incidence of alveolar histocytes in both sexes. A chronic RfD/PAD for all populations was selected from a chronic feeding study in dogs based on increased severity of chronic penumonitis and gross lung lesions in both sexes and focal pulmonary granulomas in males. Points of departure for dermal exposures utilized a dermal absorption factor of 0.3% and the same endpoints as those utilized in the dietary assessment, with the multi-generation study in rats used for short/intermediate-term dermal assessments and the chronic feeding study in dogs used for long-term dermal assessments. A subchronic inhalation study in rats was used for short thru long-term inhalation assessments. An uncertainty factor of 100x was applied to endpoints selected for all exposure routes (10x for interspecies extrapolation, 10x for intraspecies variation).

Exposure/Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary (food and water) and occupational exposure pathways based on the proposed new use of paraquat on perennial tropical and sub-tropical fruit trees. Paraquat has no residential uses; therefore, a residential assessment is not required. Refined acute and chronic dietary and drinking water risk assessments for paraquat showed that dietary and drinking water exposure estimates are below HED's level of concern for the general population and all population subgroups. Occupational exposure and risk estimates indicate that worker handler and post-application exposures are not of concern at the maximum allowable application rates for the proposed new uses. Aggregate risks are not of concern.

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix D, have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review. Although there are significant gaps in the ethical documentation for these studies, there is no evidence that the research was intended to harm participants or that it was fundamentally unethical in other ways (MRIDs 00126097, 00126098, & 00126099, K. Sherman, 6/11/2012).

2.0 HED RECOMMENDATIONS

2.1 Data Deficiencies/Conditions of Registration

Submission of a revised Section F is required. An immunotoxicity study required as part of new 40 CFR Part 158 data requirements for registration of a pesticide has been submitted and is being reviewed. Based on a preliminary review, the study is acceptable and indicates no evidence of immunotoxicity.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

PAM Vol. II lists a spectrophotometric method, designated as Method I (LOD = 0.01-0.06 ppm), as being available for the enforcement of tolerances in plant commodities. Several modifications of Method I have been developed for analysis of specific crops, and these modified methods have been used for data collection.

PAM Vol. II lists a spectrophotometric method, designated as Method Ia (LOD = 0.005 ppm), as being available for the enforcement of tolerances in animal commodities. The registrant has submitted descriptions and adequate independent laboratory validation data for a high-performance liquid chromatography method (HPLC; designated as Method 4B) to determine paraquat residues in animal tissues and eggs. The method has been validated by the Analytical Chemistry Branch (ACB). The registrant was requested to make minor changes in the method write-up. A revised version of the method has been submitted (RAM 004/04; MRID 43226902) and is now available for enforcement purposes. The reported LOQ is 0.005 ppm for livestock tissues and eggs.

2.2.2 International Harmonization

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for paraquat residues in various commodities. The Codex and U.S. tolerances are in harmony with respect to MRL/tolerance expression; both regulate the parent paraquat cation only. The Agency cannot harmonize with the Codex MRL of 0.01 ppm since some commodities which the proposed US tolerance is translated from contained residues of > 0.01 ppm. A comparison of the Codex MRLs and the proposed U.S. tolerances is presented in the following table. To the extent possible, U.S. tolerances have been harmonized with Codex, Canadian, and Mexican MRLs.

No Canadian or Mexican MRLs have been established for paraquat. Registered food/feed uses of paraquat exist in Canada. These uses presumably fall under the PMRA General MRL of 0.1 mg/kg. Regulation B.15.002(1) of the Canadian Food and Drugs Regulations (FDR) establishes 0.1 ppm as the General Maximum Residue Limit. This regulation states that a food is adulterated if it contains residues of a pesticide at a level greater than 0.1 ppm unless a specific MRL has been established in Table II, Division 15 of the FDR.

2.2.3 Recommended Tolerances

Pending the submission of a revised Section F, there are no residue chemistry issues that would preclude granting a registration for paraquat on perennial tropical and sub-tropical fruit trees, as follows:

In 2009 HED issued guidance on tolerance expressions (S. Knizner, 2009). We now conclude the tolerance expression should be as follows: *Tolerances are established for residues of paraquat, <u>including</u> its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only paraquat dichloride and calculated as the paraquat cation.*

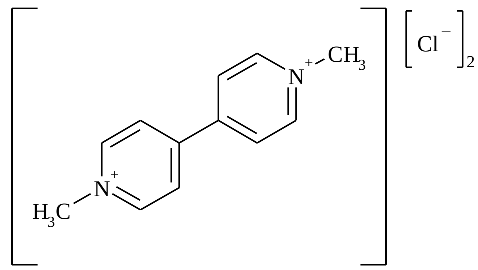
Table 1. Tolerance Summary for Paraquat Dichloride				
Commodity	Tolerance (ppm)			Comments (*correct commodity definition*)
	Established	Proposed	Recommended	
Tolerances to be established under 40 CFR ' 180.205(a):				
Atemoya	--	0.05	0.05	
Biriba	--	0.05	0.05	
Black sapote	--	0.05	0.05	*Sapote, black*
Canistel	--	0.05	0.05	
Cherimoya	--	0.05	0.05	
Custard apple	--	0.05	0.05	
Feijoa	--	0.05	0.05	
Ilama	--	0.05	0.05	
Jaboticaba	--	0.05	0.05	
Longan	--	0.05	0.05	
Lychee	--	0.05	0.05	
Mamey sapote	--	0.05	0.05	*Sapote, mamey*
Mango	--	0.05	0.05	
Pawpaw	--	0.05	0.05	
Pomegranate	--	0.05	0.05	
Pulasan	--	0.05	0.05	
Rambutan	--	0.05	0.05	
Sapodilla	--	0.05	0.05	
Soursop	--	0.05	0.05	
Spanish lime	--	0.05	0.05	
Star apple	--	0.05	0.05	
Starfruit	--	0.05	0.05	
Sugar apple	--	0.05	0.05	
Wax jambu	--	0.05	0.05	
White sapote	--	0.05	0.05	*Sapote, white*

2.2.4 Revisions to Petitioned-For Tolerances

The only revisions are for correcting the commodity definitions.

3.0 INGREDIENT PROFILE

3.1 Chemical Identity

Table 2. Nomenclature of Paraquat Dichloride.	
Compound	
Common name	Paraquat dichloride
IUPAC name	1,1'-dimethyl-4,4'-bypyridinium dichloride
CAS name	1,1'-dimethyl-4,4'-bypyridinium dichloride
CAS registry number	1910-42-5 (4685-14-7 for the cation)
End-use product (EP)	2.0 lb paraquat cation/gal SC (Gramoxone Inteon; EPA Reg. No. 100-1217)

3.2 Physical/Chemical Characteristics

A table of the physiochemical properties of paraquat dichloride is provided in Appendix B. Paraquat dichloride is freely soluble in water, slightly soluble in alcohols, and insoluble in nonpolar organic solvents. It has a very low vapor pressure.

3.3 Pesticide Use Pattern

3.3.1 Registered Products

There are currently 26 active paraquat dichloride registrations including 19 Section 3 registrations and six special local needs (SLNs) or 24(c) registrations and one Experimental Use Permit (EUP).

3.3.2 Proposed New Uses

IR-4 has submitted a petition (PP#0E7748) to support uses on perennial tropical and sub-tropical fruit trees. The product to be used is Gramoxone Inteon ® (EPA Reg. No. 100-1217), a soluble concentrate (SC) formulation which contains 2 lb paraquat cation/gal. Gramoxone Inteon ® is proposed for postemergence directed spray to the floor of orchards of perennial tropical and sub-tropical fruit trees. Maximum application rate is 0.94 lb a.i./A. A maximum of four applications is proposed along with a 14-day pre-harvest interval (PHI).

3.4 Anticipated Exposure Pathways

Dietary (food and water) exposures are expected based on existing uses of paraquat dichloride and the requested new uses. A residential exposure assessment is not required for this assessment because there are no residential uses or exposures associated with paraquat dichloride.

3.5 Considerations of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Toxicology Studies Available for Analysis

The toxicology database for paraquat dichloride is considered complete. Acute and subchronic neurotoxicity studies required by the new 40 CFR Part 158 data requirements have been submitted and reviewed by the Agency. An immunotoxicity study that was also a new data requirement has been submitted, been reviewed and acceptable. None of these recently submitted studies alter the endpoints selected for this risk assessment.

4.2 Absorption, Distribution, Metabolism and Excretion

Paraquat is poorly absorbed after oral administration to rats, dogs and mice. After oral administration (gastric intubation) of single doses of paraquat dichloride or dimethylsulfate to Wistar strain male and female rats, most of the administered radioactivity (69-96%) was excreted in feces as unchanged parent (e.g. was not metabolized). Of the fraction that was metabolized (up to 30%) the route of degradation was found to be microbial degradation of paraquat in the gut. Most of the administered dose of paraquat is excreted in the feces is excreted within 2-3 days. The excretion profile of paraquat changed markedly with the route of administration. After subcutaneous injection, unchanged paraquat appeared mostly in urine (73-96% of the administered radioactivity), where is was excreted as unchanged parent (73-96% dose) within 1 day of dosing.

The fraction of paraquat that is orally absorbed was rapidly distributed to most tissues (particularly the lungs and kidneys). Tissues other than the lungs did not retain paraquat.

4.3 Toxicological Effects

The primary target organ of paraquat is the lung. Evidence of lung inflammation, scarring, and compromised lung function in response to paraquat are observed throughout the toxicity database in different species (rats, mice, and dogs). Effects in the respiratory tract are observed after acute, subchronic, and chronic exposures regardless of the route of exposure (oral or inhalation). However, inhalation was a more sensitive route of exposure than the oral route. With increasing durations of exposure, effects of paraquat in other organ systems are observed. These effects include liver inflammation and necrosis in rats and inflammation and necrosis of the kidneys in rats and mice. Lenticular changes in the eyes of rats were also observed with increasing durations of exposure. Importantly, the lung effects occur at doses lower than effects in these other organs systems, and so protecting for lung effects protects for all other adverse effects of paraquat.

The effects of paraquat in lungs are considered systemic effects. There are no dermal toxicity studies suitable for evaluation of systemic lung effects in the toxicity database for paraquat. The only available dermal toxicity study was conducted in rabbits. Since severe skin damage resulted at relatively low topical doses (6 mg/kg), it was not possible to test doses high enough to result in systemic toxicity, particularly lung effects. Therefore, the Agency is using a dermal absorption factor of 0.3% that was derived dermal absorption studies conducted in humans and monkeys and an oral endpoint for dermal risk assessments.

Paraquat does not cause reproductive toxicity. Developmental toxicity in response to paraquat, when observed, always occurred in the presence of maternal toxicity. Four developmental toxicity studies (two in rats and two in mice) are available. If developmental toxicity was present, clear no adverse effect levels were identified which were equivalent to (or exceeded) those for maternal toxicity. Therefore, there was no evidence of quantitative susceptibility. The kinds of developmental effects observed (e.g. reduced body weight/gain and delayed skeletal ossification) are effects that commonly observed secondary to maternal toxicity. These developmental effects, when present, differed in nature but were considered of lesser severity than those observed in maternal animals (e.g. respiratory distress, reduced body weight, lesions in the lungs and kidneys). Since effects in the offspring, when present, were lesser in severity than those observed in maternal animals and were also consistent with those commonly observed as secondary to maternal toxicity, the Agency has concluded that there was no evidence of qualitative susceptibility in the young.

Previously, the Agency had required that a developmental toxicity study in rabbits be conducted for paraquat. As a result, the FQPA Safety Factor had been retained as a 3X database uncertainty factor for Females 13-39 the acute dietary risk assessment only. The Agency recently reviewed the toxicity database for paraquat and concluded that a developmental toxicity study in rabbits was not likely to add information that would impact the paraquat risk assessment. Therefore, this study is no longer required and the FQPA Safety Factor has been reduced to 1X for this population.

No evidence of neurotoxicity was observed in acute and subchronic neurotoxicity studies conducted with paraquat up to the doses at which respiratory effects were observed (e.g. the maximum tolerated dose). There was also no evidence of immunotoxicity in response to paraquat.

Paraquat was found to be weakly positive in the mouse lymphoma assay and human lymphocyte cytogenetic assay, and was positive in the sister chromatid exchange assay. Conversely, paraquat was not mutagenic in the *Salmonella typhimurium* assay, was not genotoxic in the unscheduled DNA synthesis assay *in vitro* or *in vivo,* was negative for chromosomal aberration in the bone marrow test, and no evidence was found for suppressed fertility or dominant lethal mutagenicity in mice. The Cancer Peer Review Committee and the Science Advisory Committee (1989) concluded that there was no evidence of carcinogenicity in animal studies and classified paraquat as a Group E chemical (evidence of non-carcinogenicity in humans).

Paraquat is severely toxic following acute exposure via the dermal and inhalation routes (Category I) and only slightly less toxic by the oral route of exposure (Category II). It is a dermal and ocular irritant but is not a skin sensitizer.

The complete toxicity profile for paraquat is provided in Appendix A.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The toxicological database for paraquat is complete. . Previously, the Agency had required that a developmental toxicity study in rabbits be conducted for paraquat. As a result, the FQPA Safety Factor had been retained as a 3X database uncertainty factor for Females 13-39 the acute dietary risk assessment. The Agency recently reviewed the toxicity database for paraquat and concluded that a developmental toxicity study in rabbits was not likely to add information that would impact the paraquat risk assessment (K. Rury, TXR 0056294). Therefore, this study is no longer required and the FQPA Safety Factor has been reduced to 1X for this population for the acute dietary risk assessment.

The FQPA Safety Factor remains reduced to 1X for the acute dietary assessment for the General Population and also remains reduced to 1X for the chronic dietary assessment for All Populations. Reduction of the FQPA Safety Factor to 1X is supported by: 1) No evidence of neurotoxicity in the toxicity database; 2) No indication of quantitative or qualitative susceptibility of mice or rats to *in utero* and/or pre- or post-natal exposure in five studies investigating these parameters; 3) Clear NOAELs for developmental effects, when observed; 4) A conservative dietary assessments that does not underestimate the potential exposures for infants and children; and 5) No registered or proposed residential uses for paraquat.

4.4.1 Completeness of the Toxicology Database

The toxicity database for paraquat is considered complete. Previously, the Agency had required that a developmental toxicity study in rabbits be conducted for paraquat in order to fully satisfy Part 158 data requirements. The Agency recently reviewed the toxicity database for paraquat and concluded that a developmental toxicity study in rabbits was not likely to add information that would impact the paraquat risk assessment (J. Ryman, April 14, 2012, TXR 0056294). There are five studies available in which to assess the effects of paraquat on development. There are two developmental toxicity studies conducted in rats; two developmental toxicity studies conducted in mice, and a 3-generation reproductive and developmental toxicity study conducted in rats. Guideline acute and subchronic neurotoxicity studies are also now available.

4.4.2 Evidence of Neurotoxicity

Guideline acute and subchronic neurotoxicity studies in adult rats were performed that included functional observational batteries for neurological effects and detailed histopathology of the nervous system. No evidence of neurotoxicity was observed in these studies at dose levels up to those that cause respiratory distress and death. Also, paraquat did not cause neurotoxic effects in any of the other studies in the toxicity database. The Agency as low concern for paraquat to be a developmental neurotoxicant due to an absence of neurotoxic effects in the Agency's toxicity database, together with developmental toxicity studies indicating that fetal toxicity is secondary to maternal toxicity. Due to this low concern, a developmental neurotoxicity study is not required.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Developmental toxicity in response to paraquat, when observed, always occurred in the presence of maternal toxicity. Four developmental toxicity studies (two in rats and two in mice) and a 3-generation reproduction and developmental toxicity study are available. Developmental toxicity was observed in one developmental rat study and one developmental mouse study and always occurred in the context of severe maternal toxicity (e.g. respiratory distress, reduced body weight, lesions in the lungs and kidneys). There was no quantitative susceptibility, since developmental effects were observed at the same dose that caused maternal toxicity. The kinds of developmental effects observed in these studies (e.g. reduced body weight/gain and delayed skeletal ossification) are effects that are commonly observed secondary to maternal toxicity, and clear NOAELs for developmental effects were always identified. Since effects in the offspring, when present, were lesser in severity than those observed in maternal animals and were also consistent with those commonly observed as secondary to maternal toxicity, the Agency has concluded that there was no evidence of qualitative susceptibility in the young to paraquat.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative and will not underestimate dietary and/or non-dietary residential exposure to paraquat dichloride.

4.5 Toxicity Endpoint and Point of Departure

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PODs) for dietary (food and water) and occupational scenarios are summarized below. A detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

Toxicological points of departure (PODs) were selected for dietary/drinking water and occupational exposure scenarios for this assessment. Acute and chronic reference doses (RfDs) were selected for assessment of food and drinking water exposures. The population adjusted dose (PAD) is equivalent to the reference dose (RfD) divided by the additional FQPA Safety

Factor, which was reduced to 1X for All Populations. An acute RfD/PAD for all populations was selected from a multi-generation study in rats which showed increased incidence of alveolar histocytes in both sexes. A chronic RfD/PAD for all populations was selected from a chronic feeding study in dogs based on increased severity of chronic penumonitis and gross lung lesions in both sexes and focal pulmonary granulomas in males. Points of departure for dermal exposures utilized a dermal absorption factor of 0.3% and the same endpoints as those utilized in the dietary assessment, with the multi-generation study in rats used for short/intermediate-term dermal assessments and the chronic feeding study in dogs used for long-term dermal assessments. A subchronic inhalation study in rats was used for short thru long-term inhalation assessments. An uncertainty factor of 100x was applied to endpoints selected for all exposure routes (10x for interspecies extrapolation, 10x for intraspecies variation).

4.5.2 Recommendations for Combining Exposure Routes

The acute and chronic aggregate exposure assessments for all population subgroups include only food and water exposures. There are currently no residential uses for paraquat and there are no short- or intermediate-term exposure scenarios. Therefore, non-occupational short- and intermediate-term aggregate risk assessments were not conducted.

For occupational assessments, the toxic endpoint of concern (e.g. lung effects) is the same for both inhalation and dermal routes of exposure. Therefore, these routes should be aggregated when assessing worker risks.

4.5.3 Classification of Carcinogenic Potential

Paraquat is currently placed in Category E (evidence of non-carcinogenicity to humans). The carcinogenic potential of paraquat was evaluated by the Toxicology Branch Peer Review Committee (now Carcinogenicity Assessment Review Committee (CARC)) in 1986, 1988, and 1989, and by the Scientific Advisory Panel (SAP) in 1989. In 1986 the CARC classified paraquat as a Category C carcinogen (limited evidence of carcinogenicity in animals), based on an apparent increase in erroneously combined squamous cell carcinomas in different locations in the head region. In February of 1989 the SAP classified paraquat as Category D (equivocal evidence of carcinogenicity) based on squamous cell carcinoma in the nasal cavity of 2 high-dose rats. However, the SAP also commented that endpoints other than carcinogenicity were more relevant for the regulation of paraquat. Finally, in the following month (March of 1989) the CARC placed paraquat in Category E (as it had done the previous year, 1988). As a result, for this human health risk assessment, paraquat is classified in Category E, i.e., there is evidence of non-carcinogenicity to humans.

Paraquat was found to be weakly positive in the mouse lymphoma assay and human lymphocyte cytogenetic assay and was positive for sister chromatid exchange assay. Conversely, paraquat was not mutagenic in the *Salmonella typhimurium* assay, not genotoxic in the unscheduled DNA synthesis assay *in vivo* or *in vitro*, negative for chromosomal aberration in the bone marrow test, and no evidence was found for suppressed fertility or dominant lethal mutagenicity in mice.

4.5.4 Summary of Points of Departure Used in Risk Assessment

Toxicological doses/endpoints selected for the paraquat risk assessment are provided in Table 3.

Table 3. Summary of Toxicological Doses and Endpoints for Paraquat for Use in Human Health Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	NOAEL = 1.25 mg/kg/day UF = 100 Acute RfD = 0.0125 mg/kg/day	FQPA SF = 1x aPAD = 0.0125 mg/kg/day	Multi-generation rat study LOAEL = 3.75 mg/kg/day, based on increased incidences of alveolar histiocytes in both sexes
Chronic Dietary (all populations)	NOAEL = 0.45 mg/kg/day UF = 100 Chronic RfD = 0.0045 mg/kg/day	FQPA SF = 1x cPAD = 0.0045 mg/kg/day	Chronic toxicity in dogs LOAEL = 0.93 mg/kg/day, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males
Dermal Short- - Intermediate - Term (1day – 6 months)	NOAEL = 1.25 mg/kg/day	LOC = MOE = 100 Dermal absorption factor = 0.3%	Multi-generation rat study LOAEL = 3.75 mg/kg/day, based on increased incidences of alveolar histiocytes in both sexes
Dermal Long-Term (> 6 months)	NOAEL = 0.45 mg/kg/day	LOC = MOE = 100 Dermal absorption factor = 0.3%	Chronic toxicity in dogs LOAEL = 0.93 mg/kg/day, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males
Inhalation Short - through Long - Term (1 day - > 6 months)	NOAEL = 0.01 µg/L for respirable particles NOAEL = 1.25 mg/kg/day for non-respirable particles	LOC = MOE = 100 Inhalation absorption factor = 100%	21-Day inhalation toxicity study in rats (respirable particles) LOAEL = 0.10 µg/L, based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx 3-generation reproduction study (non-respirable particles)
Cancer (oral, dermal, inhalation)	**Classification:** Category E (evidence of non-carcinogenicity to humans)		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
* Refer to Section 3.5

5.0 DIETARY AND DRINKING WATER EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant Metabolism Studies

The residue chemistry chapter of the paraquat RED (D217262, D. Miller, 7/28/95) concluded that, for the purposes of reregistration and risk assessment, the qualitative nature of the residue in plants is adequately understood based on studies depicting the metabolism of paraquat in carrots and lettuce following preemergence treatment and in potatoes and soybeans following desiccant treatment. The residue of concern in plants is parent paraquat.

5.1.2 Comparison of Metabolic Pathways

Paraquat is very stable. In both primary crops and rotational crops, parent paraquat was the only major residue. In goats, pigs, and poultry, paraquat was again the only residue of concern. Paraquat was not metabolized by rats. Paraquat was poorly absorbed after oral administration to rats, dogs and mice. Once absorbed, paraquat was rapidly distributed to most tissues but especially to lungs and kidneys. Tissues other than lungs did not retain paraquat. In the environment, paraquat is very persistent and undergoes minimal degradation. As a result of the findings of the plant and animal metabolism studies as well as the environmental degradation studies, parent paraquat is the only residue of concern considered in this human health risk assessment.

5.1.3 Environmental Fate and Transport

Paraquat undergoes minimal degradation in the environment, and thus is very persistent (as parent). However, its very high propensity to bind to solids, particularly clay, makes it very immobile. In addition, paraquat does not readily appear to desorb from clay. The greatest cause for concern is likely to be erosion of contaminated sediments off-site and subsequent redeposition onto non-target areas (especially surface water bodies). There is an additional (minor) concern for the one proposed new usage (wheat) that includes aerial spray; however, this use entails very small amounts (relative to all other uses), so spray drift onto nearby surface water drinking water sources should be fairly limited. Because of its very low mobility and strong tendency to bind tightly to soils, paraquat contamination of drinking water supplies derived from groundwater is expected to be highly unlikely. In addition, the strong binding characteristics of paraquat are likely to render most residues in raw drinking water sources removable through sedimentation processes, which are typically included as part of standard drinking water treatments.

5.1.4 Residues of Concern Summary and Rationale

The residue chemistry chapter of the RED (D217262, D. Miller, 7/28/95) concluded that for purposes of reregistration and risk assessment, the qualitative nature of the residue in plants and livestock is adequately understood based on the combined results of metabolism studies. The residue of concern is parent paraquat.

Table 4 provides a summary of the MARC decisions regarding residues of concern for paraquat.

Table 4. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent Paraquat	Parent Paraquat
	Rotational Crop	Parent Paraquat	Parent Paraquat
Livestock	Ruminant	Parent Paraquat	Parent Paraquat
	Poultry	Parent Paraquat	Parent Paraquat
Drinking Water		Parent Paraquat	N/A

5.2 Food Residue Profile

5.2.1 Residues in Crops

No residue field trial data have been submitted for this petition. The following was taken from the minutes of the 10/1/2008 ChemSAC meeting.

3. Paraquat on Tropical Fruits (IR-4 via M. Doherty):

IR-4 is requesting that EPA allow tolerances and registrations on all perennial tropical fruit crops based on surrogate data and current registrations. Specifically, IR-4 requests 0.05 ppm tolerances and registrations for the following perennial tropical and semi-tropical fruit trees: sugar apple, cherimoya, atemoya, custard apple, ilama, soursop, birba, lychee, longan, Spanish lime, rambutan, pulasan, star apple, black sapote, mango, sapodilla, canistel, mamey sapote, feijoa, jaboticaba, wax jambu, starfruit (carambola), pawpaw, pomegranate, and white sapote.

The proposed use pattern for the perennial tropical fruit crops will be the same as for the following currently labeled perennial crops: avocado, acerola, banana, papaya, guava, coffee, tree nuts, fig, citrus fruit, pome fruit, olive, persimmon, and stone fruit (Gramoxone label), which all have a tolerance of 0.05 ppm.

Passionfruit, a tropical fruit crop, is an exception with a tolerance of 0.2 ppm. Passionfruit differs from the rest in that it is a vine which drops ripe fruit to the ground; much of the fruit is harvested by picking it up off the ground.

The ChemSAC had no objection to the proposal.

5.3 Water Residue Profile

5.3.1 Estimated Drinking Water Concentrations

The drinking water estimates used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED; Memo, J. Lin, 10-January-2012; D396402). EFED reviewed a non-guideline supplemental mobility study (MRID 48659501). The submitted study was conducted to evaluate the effects of traditional water treatment processes on paraquat and to determine the mobility of paraquat through soil filtration column. This memorandum only addresses the first aspect on the effects of using jar tests as a mean to mimic traditional water treatment processes to determine whether the results of jar tests are sufficient to provide the justification to refine the previous drinking water assessment (J. Lin, 11-May-2011; D381972).

^{14}C-paraquat, spiked at ~30 ppb into the raw surface water samples from five representative US CWS (community water supply) facilities, was effectively removed by a combination of typical water treatment processes conducted on a laboratory-scale: the “laboratory jar test” (coagulation using alum with either lime or soda ash, flocculation and sedimentation), followed by duel media filtration (anthracite atop of filtering sand). The combination process was able to reduce the level of ^{14}C-paraquat to approximate or below the limit of detection of about 0.15µg/L (ppb). The jar test results allow EFED to better characterize potential levels in finished water for drinking water assessment purpose. The level of paraquat in the finished water of 0.15 µg/L should be used for the drinking water assessment.

5.4 Dietary and Drinking Water Exposure and Risk

Refined acute and chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional Safety Factor, if applied. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.4.1 Acute Dietary and Drinking Water Analysis

A refined (probabilistic) acute dietary exposure analysis was performed for the general population and all population subgroups. The acute analysis assumed a distribution of residues based on tolerance level residues. Empirical and DEEM default processing factors were used to modify the field trial data. Maximum screening-level percent crop treated estimates were used for commodities for which data were available. If no percent crop treated data were available, 100% crop treated was assumed. The acute analysis incorporated the jar test result concentration of 0.15 ppb for the drinking water residue. Acute dietary risk estimates are not of concern for general population or other population subgroups. The subgroup with the highest risk estimate was children 3-5 years old with a 99.9th percentile acute exposure estimate of 35% of the aPAD. The 99.9th percentile aPAD for the general U.S. population was 17%.

Table 5. Results of Acute Dietary Exposure Analysis for Paraquat (Food and Drinking Water)			
Population Subgroup	**aPAD (mkd)***	**99.9th Percentile**	
		Exposure (mkd)	**% aPAD**
General U.S. Population	0.0125	0.004381	8
All Infants (< 1 year old)	0.0125	0.007936	13
Children 1-2 years old	0.0125	**0.008897**	21
Children 3-5 years old	0.0125	0.006969	16
Children 6-12 years old	0.0125	0.005348	10
Youth 13-19 years old	0.0125	0.003615	6
Adults 20-49 years old	0.0125	0.002745	5
Adults 50+ years old	0.0125	0.002463	5
Females 13-49 years old	0.0042	0.002644	15

*mkd: milligram per kilogram per day

5.4.2 Chronic Dietary and Drinking Water Analysis

A conservative chronic dietary exposure analysis was performed for the general U.S. population and various population subgroups. Tolerance level residues and average percent crop treated assumptions were used. DEEM default and empirical processing factors were used to modify the tolerance values. The acute analysis incorporated the jar test result concentration of 0.15 ppb for the drinking water residue. The population subgroups females 13-49 and young children had a more protective chronic population adjusted dose (cPAD, 0.082 mg/kg/day) than the general U.S. population and all other population subgroups (0.25 mg/kg/day). Chronic dietary risk estimates are not of concern for general population or other population subgroups. The subgroups with the highest risk estimate were children 1-2 and 3-5 years old with a cPAD of 11%. The % cPAD for the general U.S. population was 4%.

Table 6. Results of Chronic Dietary Exposure Analysis for Paraquat (Food and Drinking Water)			
Population Subgroup	**cPAD (mkd)***	**Exposure (mkd)**	**% aPAD**
General U.S. Population	0.0045	0.000197	4
All Infants (< 1 year old)		0.000342	8
Children 1-2 years old		**0.000645**	**14**
Children 3-5 years old		0.000493	11
Children 6-12 years old		0.000293	7
Youth 13-19 years old		0.000164	4
Adults 20-49 years old		0.000147	3
Adults 50+ years old		0.000140	3
Females 13-49 years old		0.000140	3

6.0 RESIDENTIAL EXPOSURE AND RISK ASSESSMENT

Residential exposures and risk are not assessed in this document because the proposed uses of paraquat do not involve applications by homeowners or commercial applicators in residential settings at this time and there are no existing residential uses.

6.1 Residential Bystander Postapplication Inhalation Exposure

There are no residential uses proposed for paraquat in this registration action, therefore a residential exposure assessment was not conducted.

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for paraquat at this time. However, volatilization of pesticides may be a potential source of post-application inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html) and is in the process of evaluating the SAP report. The Agency may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for paraquat.

6.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for acibenzolar S-methyl. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

Although a quantitative residential post-application inhalation exposure assessment was not performed as a result of pesticide drift from neighboring treated agricultural fields, an inhalation exposure assessment was performed for flaggers. This exposure scenario is representative of a worse case inhalation (drift) exposure and may be considered protective of most outdoor agricultural and commercial post-application inhalation exposure scenarios.

7.0 AGGREGATE EXPOSURE AND RISK ASSESSMENT

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Since there are no residential uses of paraquat the acute and chronic aggregate exposures include food plus drinking water exposures. Acute and chronic aggregate risks are not of concern.

7.1 Short-, Intermediate-, and Long-Term Aggregate Risk

There are no current or proposed residential uses of paraquat. Therefore, the acute and chronic exposure estimates provided in the dietary and drinking water exposure section represent aggregate exposure.

8.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide's residues and “other substances that have a common mechanism of toxicity.”

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to paraquat and any other substances, and paraquat does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that paraquat has a common mechanism of toxicity with other substances. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA’s Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA’s website at http://www.epa.gov/pesticides/cumulative/.

9.0 OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION

9.1 Exposure Scenarios

Occupational handler and post-application exposure scenarios were assessed for the proposed use of paraquat on perennial tropical and sub-tropical fruit trees. Based on the product labels and information provided by the registrant, short- and intermediate-term exposure is assessed for occupational handlers and post-application activities. Dermal and inhalation exposures to workers are aggregated for paraquat because the toxicity endpoints for these exposure routes are based on common toxicological effects.

9.2 Handler Exposure

The term “handler” applies to individuals who mix, load, and apply the pesticide product. The following handler exposure scenarios were assessed for the proposed new uses.

9.2.1 Handler Exposure Scenarios

Occupational handler and post-application exposure scenarios were assessed for the proposed use of paraquat on perennial tropical and sub-tropical fruit trees. Based on the product labels and information provided by the registrant, short- and intermediate-term exposure is assessed for occupational handlers. The term “handler” applies to individuals who mix, load, and apply the pesticide product. The following handler exposure scenarios were assessed for the proposed new uses.

MIXER/LOADER

1. Open mixing/loading for groundboom applications;

MIXER/LOADER/APPLICATOR

1. Open mixing/loading/applying for backpack sprayer applications.

APPLICATORS

1. Applying sprays with groundboom equipment.

9.2.2 Handler Exposure Data

No chemical-specific handler exposure data were submitted in support of this registration. It is the policy of the HED to use surrogate data from the US Environmental Protection Agency, Office of Pesticide Programs, Occupational Pesticide Handler Unit Exposure Surrogate Reference Table, June 21, 2011, which summarizes and extracts surrogate data from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database, and the Outdoor Residential Exposure Task Force (ORETF) database. Some of these data, such as the industry task force data, are compensatory, subject to the data protection provisions of FIFRA. HED policies on use of surrogate data, including their sources, are presented on the internet at http://www.epa.gov/pesticides/science/handler-exposure-data.html . The "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" may be found at http://www.epa.gov/pesticides/science/handler-exposure-table.pdf.

9.2.3 Handler Exposure Assumptions

Unit Exposures

No chemical-specific handler exposure data were submitted in support of this registration. In the absence of chemical-specific data, it is the policy of HED to use the best available surrogate data. Sources of surrogate data include PHED 1.1, the AHETF database, the ORETF database, or other proprietary occupational exposure studies. Some of these data, such as the industry task force data, are compensatory, subject to the data protection provisions of FIFRA. Default exposures used in this analysis are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (http://www.epa.gov/opp00001/science/handler-exposure-table.pdf), which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/handler-exposure-table.pdf.

Area/Amount Treated

Based on HED ExpoSAC Policy No. 9.1, the area treated in a day was assumed to be:

- 80 acres for mixing/loading to support groundboom applications,
- 80 acres for applying with groundboom equipment.
- 5.0 acres for mixing/loading/applying backpack sprayer applications,

Application Rate
The maximum single application rate is (0.94 lb ai/A) for groundboom, and (0.50 lb ai/A) for backpack sprayer applications. Applications may be reapplied up to 4 times per season.

Label directions: *Maximum Application Rates*
- 3.75 pts = (0.94 lbs. a.i/Acre) for groundboom.
- 2.5 pts = (5.0 lbs a.i./Acre) for backpack sprayer.

Body Weight
The average adult body weight of 80 kg was used for estimating short-term dermal and inhalation daily dose calculations.

Absorption Factors
Since the short- and intermediate-term dermal PoD was based on a 21 day inhalation study, therefore a 0.3% dermal absorption factor was used to estimate dermal exposure, and 100% absorption was assumed for estimating inhalation exposure.

Equations and Calculations

Daily Dose:
Daily dose (dermal and inhalation) is calculated by normalizing the daily exposure (dermal or inhalation) value by body weight and accounting for absorption factors:

$$\text{Average Daily Dose (mg/kg/day)} = \text{Daily Exposure (mg ai/day)} \times \left\{\frac{\text{Absorption Factor}}{\text{Body Weight (kg)}}\right\}$$

Where:
Average Daily Dose = Absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day),

Daily Exposure = Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption,

Absorption Factor = A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs, and

Body Weight = Body weight determined to represent the population of interest in a risk assessment.

Margin of Exposure (MOE):
The daily dermal and inhalation dose received by occupational handlers was compared to the appropriate PoD (i.e. NOAELs) to assess the risk to occupational handlers. All MOE values were calculated using the following formula:

$$MOE = \frac{\text{NOAEL (mg/kg/day)}}{\text{Average Daily Dose (mg/kg/day)}}$$

Where:

MOE = Margin of exposure value used by HED to represent risk or how close a chemical exposure is to being a concern (unitless),

ADD = Average daily dose (ADD) is absorbed dose received from exposure to pesticide, and

NOAEL = Dose level in a toxicity study, where no observed adverse effects occurred in the study.

Combined Risk Estimates

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for the dermal and inhalation routes were the same. Dermal and inhalation risks were combined using the following formula:

Total MOE = 1 / (1/Dermal MOE) + (1/ Inhalation MOE)

9.2.4 Handler Exposure and Risk Estimates

Margin of Exposure calculations for groundboom and backpack sprayers were impacted due to updated unit exposures for the proposed uses, however for the exposure scenarios listed within (mixing/loading and applying, and mixing/loading/applying by the same worker), risk estimates do not exceed HED's LOC (MOE < 100), and therefore are not of concern to HED. See Table 13 for details.

Table 13: Occupational Short and Intermediate-Term Risk Assessment/Amended Uses of Paraquat								
Exposure Scenario	Crops	Application. Rate	Area Treated	Inhalation Unit Exp.	Dermal Unit Exp.	Inhalation Daily Dose	Dermal Daily Dose	Combined MOE[5] Short/Int-term
		(lb a.i/A)[1]	(A/day)[2]	(µg/lb ai)[3]	(µg/lb ai)[3]	(mg/kg/day)[4]	(mg/kg/day)[4]	Baseline (Dermal+ Inhalation)
Mixer/Loader *(soluble concentrate)* [6]								
Groundboom	Perennial Tropical and Sub-Tropical Fruit Trees	0.94	80	0.219	220	0.0002	0.0006	1500
Applying (*soluble concentrate)*								
Groundboom (Open Cab)	Perennial Tropical and Sub-Tropical Fruit Trees	0.94	80	0.34	79	0.0003	0.0002	2,300
Mixing/Loading/Applying *(soluble concentrate)*								
Backpack Sprayer	Perennial Tropical and Sub-Tropical Fruit Trees	0.5	5	2.6	8.3	0.0001	0.0008	1,500

1. Application rates are based on maximum values found in proposed labels: Gramoxone Inteon®; Express®, and SL® (EPA Registration Number 100-1217)
2. Daily area treated is based on the area that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (standard EPA/OPP/HED values).
3. HED policies on use of surrogate data, including their sources, are presented in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (http://www.epa.gov/pesticides/science/handler-exposure-table.pdf) and (http://www.epa.gov/pesticides/science/handler-exposure-data.html)
4. Daily Dose (mg/kg/day) was calculated by: [(Unit Exposure * 0.3% * Appl. rate * Area treated) / 80 kg].
5. Short-/Intermediate-Term Combined MOE = Dermal + Inhalation. Short and Intermediate-term endpoints are the same [(NOAEL 1.25 mg/kg/day)], thus one column. The LOC for the target MOE = 100.
6. Note: Open mixing and loading formulation was calculated using a "soluble concentrate" exposure scenario. See PHED version 1.1 for details.

Personal Protective Equipment (PPE)

For pesticide handlers, this assessment presents "baseline" (i.e. workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes, plus socks and no protective gloves or respirators) estimates for both dermal and inhalation exposure.

However, label specifications state that applicators and handlers must wear a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes, plus socks, chemical resistant gloves, protective eyewear, and a dust mist NIOSH approved respirator (N, R, P, or HE filter). Furthermore; for mixers and loaders, a chemical resistant apron and a face shield rather than “protective eyewear” is required.

No chemical-specific handler exposure data were submitted in support of this registration. To assess handler exposures for regulatory actions when chemical-specific monitoring data are not available, HED relies on the most scientifically-reliable surrogate data currently available from various sources such as the Pesticide Handlers Exposure Database (PHED), and the Agricultural Handler Exposure Task Force (AHETF). Some of this data, such as the industry task force data, is compensatory, subject to the data protection provisions of FIFRA. HED policies on use of surrogate data, including their sources, are presented in the “Occupational Pesticide Handler Unit Exposure Surrogate Reference Table” (http://www.epa.gov/pesticides/science/handler-exposure-table.pdf) and (http://www.epa.gov/pesticides/science/handler-exposure-data.html).

Maximum Application Rates

- The label-specified amount of Paraquat to perennial tropical and sub-tropical fruit trees via groundboom was (0.94 lbs ai/Acre)

- The label-specified amount of Paraquat to treat perennial tropical and sub-tropical fruit trees via backpack sprayer application was (0.5 lbs ai/Acre).

Amount Treated

- Groundboom applications to perennial tropical and sub-tropical fruit trees: 80 Acres/Day
- Backpack applications to perennial tropical and sub-tropical fruit trees: 5 Acres/Day

9.3 Post Application Exposure

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as a re-entry exposure). Such exposure may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pest or harvesting. In the case for paraquat, post-application dermal exposure to field workers following ground applications is not probable, whereas paraquat is an herbicide that is directed at the ground/soil for use on grasses and weeds under and around fruit trees. Since no post-application data were submitted in support of the registration action, dermal exposures during post-application activities were estimated using dermal transfer coefficients from the Science Advisory Council for Exposure Policy Number 3 (http://www.epa.gov/pesticides/science/exposac_policy3.pdf), and summarized in Table 14 below. For further explanation of post-application activities and calculations, see memorandum; (J. Miller, 09/13/11, D387841) for details.

Based on the Agency's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for paraquat at this time; an inhalation exposure assessment was performed for occupational handlers. **This assessment resulted in risk estimates that did not exceed HED’s level of concern at baseline inhalation PPE.** Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. However, there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and re-suspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for paraquat.

9.3.1 Post Application Exposure Scenarios

- Handweeding, propping, orchard maintenance, and bird control
- Transplanting
- Scouting, hand pruning, and training

9.3.2 Post Application Exposure Assumptions

Equations/Calculations

The following equations were used to calculate risk estimates for workers performing post-application activities:

$$DFR_t\ (\mu g/cm^2) = AR\ (lb\ ai/acre) \times F \times (1\text{-}D)^t \times 4.54E8\ \mu g/lb \times 2.47E\text{-}8\ acre/cm^2$$

Where:

- DFR_t = dislodgeable foliage residue on day "t" ($\mu g/cm^2$),
- AR = application rate (lb ai/acre),
- F = fraction of ai retained on foliage (unitless), and
- D = fraction of residue that dissipates daily (unitless).

$$DD_t\ (mg/kg\text{-}day) = \frac{DFR_t\ (\mu g/cm^2) \times 1E\text{-}3\ mg/\mu g \times TC\ (cm^2/hr) \times DA\ (\%) \times ET\ (hrs)}{BW\ (kg)}$$

Where:

- DD_t = daily dermal dose on day "t,"
- t = number of days after application day (days),
- DFR_t = dislodgeable foliage residue on day "t" ($\mu g/cm^2$),
- TC = transfer coefficient (cm^2/hr),
- DA = dermal absorption factor (unitless),

ET = exposure time (hr/day), and
BW = body weight (kg).

$$\text{Margin of Exposure (MOE)} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Average Daily Dose (mg/kg/day)}}$$

Where:
MOE = Margin of exposure value used by HED to represent risk or how close a chemical exposure is to being a concern (unitless),
ADD = Average daily dose (ADD) is absorbed dose received from exposure to pesticide, and
NOAEL = Dose level in a toxicity study, where no observed adverse effects occurred in the study.

In addition to the maximum dermal TCs (summarized in Table 5), the following assumptions were used in the post-application assessment:

- Max Application Rate = 0.94 lb ai/A for proposed new use on Perennial Tropical and Sub-Tropical Fruit Trees,
- Exposure Duration = 8 hours per day,
- Body Weight = 80 kg for average adult for short-/intermediate-term durations,
- Dermal Abs. Factor = 0.3%
- Fraction ai retained on foliage. = (2.11 ug/cm^2) on day zero.

9.3.3 Post-Application Exposure and Risk Estimates

A target LOC or MOE of 100 is considered adequate for dermal exposure. Exposure and risk estimates indicate HED's LOC (MOE < 100), and therefore are not of concern to HED at the maximum use rate for occupational post-application exposure activities for the proposed new uses. A summary of post-application exposure and risk calculations, assumptions, and results is provided in Table 14.

Table 14. Summary of Estimated Post-application MOEs for Agricultural Crops						
Crop	**Application Rate (lb ai/A)** [1]	**DAT**[2]	**DFR** [3] **(µg/cm^2)**	**TC** [4] **(cm^2/hr)**	**Activity** [4]	**Short-/Int-Term MOE** [5]
Perennial Tropical and Sub-Tropical Fruit Trees	0.94	0	2.11	100	Hand weeding. Propping, Orchard Maintenance, Bird Control	19,800
				230	Transplanting	8,600
				580	Scouting, Hand Pruning, Training	3,400

1. Maximum application rate from proposed label: Gramoxone Inteon®; Express®, and SL® (EPA Registration Number 100-1217)
2. DAT = Days after treatment needed to reach the LOC of 100; DAT 0 = the day of treatment/ assumed to be approx. 12 hours.
3. DFR (µg/cm^2) = dislodgeable foliar residues corresponding to DAT, based on 20% of application rate.
4. TC (cm^2/hr) = transfer coefficients and associated activities from ExpoSAC Policy Number 3 (http://www.epa.gov/pesticides/science/exposac_policy3.pdf)
5. MOE = MOE on the corresponding DAT. MOE = NOAEL / Daily Dose.
   Daily Dose = [(DFR x TC x 0.3% Dermal absorption x 8-hr Exposure Time)] / [(CF: 1000 µg/mg) x (80-kg Body Weight)
   Short-/intermediate-term NOAEL = 1.25 mg/kg/day. The LOC is 100

9.3.4 Restricted Entry Interval

Paraquat has been classified in Toxicity Category III for acute dermal; a Category I for eye irritation, and negative for primary skin irritation. Per the Worker Protection Standard (WPS), a 24-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III/IV.

10. REFERENCES

Paraquat Dichloride. Request to Add Uses on Perennial Tropical and Sub-Tropical Fruit Trees, T. Morton, D381971, 6/21/2012.

Paraquat Dichloride: Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Registration Request to Add Use on Perennial Tropical and Sub-Tropical Fruit Trees., T. Morton, D387271, 5/31/2012

Paraquat: Occupational Risk Assessment for the Use on Perennial Tropical and Sub-Tropical Fruit Trees., J.S. Miller, D401017, 6/21/2012.

Review of Jar Test Results for Drinking Water Assessment Purpose – J. Lin, D396402, 1/10/12

APPENDICES

A TOXICOLOGY DATA SUMMARY

A.1 Guideline Data Requirements

Guideline No.	Study Type	Technical		MRID No.
		Required	Submitted	
870.3100	Subchronic (Oral) Toxicity - Rodent...........................	N	N	
870.3150	Subchronic (Oral) Toxicity - Non-Rodent	Y	Y	00072416
870.3200	21/28-Day Dermal Toxicity	N	Y	Acc.260635
870.3250	90-Day Dermal Toxicity	N	N	
870.3465	90-Day Inhalation Toxicity	N	Y	00113718
870.3700a	Prenatal Developmental Toxicity - Rodent	Y	Y	00113714 43964701 00096338 43949902
870.3700b	Prenatal Developmental Toxicity - Non-Rodent	Y	N	
870.3800	Reproduction and Fertility Effects	Y	Y	00126783 00149748 00149749
870.4100a	Chronic (Oral) Toxicity - Rodent................................	Y	N	
870.4100b	Chronic (Oral) Toxicity - Non-Rodent (Dog)	Y	Y	00132472
870.4200a	Carcinogenicity - Rat………………..........................	Y	N	
870.4200b	Carcinogenicity - Mouse	Y	Y	00087924 40202403
870.4300	Combined Chronic Toxicity /Carcinogenicity- Rat	Y	Y	40218001 00138637
870.6100a	Neurotoxicity - Acute Delayed Neurotox.- Hen..........	N	N	
870.6100b	Neurotoxicity - Subchronic - Hen	N	N	
870.6200a	Neurotoxicity - Acute - Rat..	Y	Y	47794201
870.6200b	Neurotoxicity -Subchronic - Rat	Y	Y	47794202
870.6300	Developmental Neurotoxicity………………	N	N	
870.7800	Immunotoxicity………………………..	Y	Y*	48667301

* Studies have been submitted and are under review

A.2 Toxicity Profiles

Table 3.1.a. Acute Toxicity Profile – Paraquat Dichloride				
Guideline No.	**Study Type [species]**	**MRID(s)**	**Results [a]**	**Toxicity Category**
870.1100	Acute oral [rat]	00054573 43685001	LD_{50} = 189 (M) or 125 (F) mg/kg	II
870.1200	Acute dermal [rabbit]	00054574	LD_{50} = 174 mg/kg (M)	I
870.1300	Acute inhalation [rat] [b]	00046105	LC_{50} = 1 μg/L (M/F)	I
870.2400	Acute eye irritation [rabbit]	00054575	Severe irritation	I
870.2500	Acute dermal irritation [rabbit]	00054576	Slight to severe irritation; PIS = 2.1	III
870.2600	Skin sensitization [guinea pig]	00155289	Negative	--

a The test material used in the acute inhalation study was crystalline paraquat dichloride. Purity was not specified, but the purity of crystalline paraquat dichloride used in other studies was 99.9%. The test material used in the other studies was paraquat dichloride in the form of ORTHO Paraquat Concentrate 3 (end use product containing 34.4% paraquat cation). Results are expressed in terms of paraquat dichloride rather than paraquat cation.

b The acute dermal (43685002), eye (43685003) and dermal (43685004) irritation and sensitization (43685005) studies are not displayed above since these studies resulted in lower toxicity and thus reduced toxicity category, likely due to a less percent of active ingredient used in the studies (D217134).

Table 3.1.b. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3150 90-Day oral toxicity Beagle dog	MRID 00072416 (1981) Acceptable/guideline 0, 7, 20, 60, or 120 ppm (estimated to be 0, 0.2, 0.5, 1.5, and 3 mg/kg/day)	NOAEL = 0.5 mg/kg/day LOAEL = 1.5 mg/kg/day, based on increased lung weight and incidence of alveolitis in both sexes
870.3200 21-Day dermal toxicity New Zealand White rabbit	MRID # not provided (Accession # 260635) (1986) Acceptable/guideline 0, 0.50, 1.15, 2.60, or 6.00 mg/kg/day	Dermal NOAEL = 1.15 mg/kg/day. Dermal LOAEL = 2.60 mg/kg/day, based on small scabs at the treatment site in both sexes and epidermal erosis/ulceration, surface exudation, acanthosis, and/or inflammation in males Systemic NOAEL = 6 mg/kg/day Systemic LOAEL = not observed
870.3465 21-Day inhalation toxicity Sprague-Dawley rat	MRID 00113718 (1979) Acceptable/guideline 0, 0.012, 0.112, 0.487, and 1.280 μg/L	NOAEL = 0.012 μg/L. LOAEL = 0.112 μg/L, based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx.
870.3700a Prenatal developmental Wistar rat	MRID 00113714 (1978) (initial study) Acceptable/guideline 0, 1, 5, or 10 mg/kg/day	Maternal NOAEL = 1 mg/kg/day. Maternal LOAEL = 5 mg/kg/day, based on mortality, clinical signs of toxicity (piloerection, hunched posture, respiratory distress), microscopic lesions in the lungs and kidney, and decreased body weight gain (BWG). Developmental NOAEL = 1 mg/kg/day. Developmental LOAEL = 5 mg/kg/day, based on slightly decreased fetal body weights and on delayed ossification.
870.3700a Prenatal developmental Wistar rat	MRID 43964701 (1992) (subsequent study) Acceptable/guideline 0, 1, 3, or 8 mg/kg/day	Maternal NOAEL = 8 mg/kg/day (highest dose tested). Maternal LOAEL = not observed. Developmental NOAEL = 8 mg/kg/day (highest dose tested). Developmental LOAEL = not observed.
870.3700a Prenatal developmental SPR Alderley Park mice	MRID 00096338 (1978) (initial study) Acceptable/guideline 0, 1, 5, or 10 mg/kg/day	Maternal NOAEL = 1 mg/kg/day. Maternal LOAEL = 5 mg/kg/day based on decreased body weight gains. Developmental NOAEL = 10 mg/kg/day. Developmental LOAEL = not observed.
870.3700a Prenatal developmental Crl:CD-1 (ICR) BR mice	MRID 43949902 (1992) (subsequent study) Acceptable/guideline 0, 7.5, 15, or 25 mg/kg/day	Maternal NOAEL =15 mg/kg/day. Maternal LOAEL = 25 mg/kg/day based on mortality, clinical signs of toxicity (piloerection, labored respiration, hunched posture, hypothermia,

Table 3.1.b. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
		hypoactivity, and/or pale extremities and eyes), decreased body weights and body weight gains, increased lung weights, and gross lesions in the lung. Developmental NOAEL = 15 mg/kg/day. Developmental LOAEL = 25 mg/kg/day based on retardation of the skeleton and decreased fetal body weights.
870.3800 Reproduction and fertility effects (3-generation) Wistar rat	MRID 00126783, 00149748, and 00149749 (1982) Acceptable/guideline 0, 25, 75, or 150 ppm (approximately equivalent to 0, 1.25, 3.75, and 7.5 mg/kg/day)	NOAEL = 1.25 mg/kg/day LOAEL for parental toxicity = 3.75 mg/kg/day, based on increased incidences of alveolar histiocytes. Offspring NOAEL = 7.5 mg/kg/day. Offspring LOAEL = not observed. Reproductive NOAEL = 7.5 mg/kg/day. Reproductive LOAEL = not observed.
870.4100b Chronic toxicity Beagle dog	MRID 00132472 (1983) Acceptable/guideline 0/0, 0.45/0.48, 0.93/1.00, or 1.51/1.58 mg/kg/day in males/females	NOAEL = 0.45/0.48 mg/kg/day in males/females LOAEL = 0.93/1.00 mg/kg/day in males/females, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males
870.4200b Carcinogenicity mouse	MRID 00087924 (1981) Acceptable/guideline 0, 0 (two controls), 12.5, 37.5, or 100/125 ppm (estimated to be 0, 0, 1.9, 5.6, and 15.0/18.8 mg/kg/day)	NOAEL = 1.9 mg/kg/day. LOAEL = 5.6 mg/kg/day, based on decreased body weights and food consumption in females, and increased incidences of renal tubular necrosis, tubular dilatation, and interstitial nephritis in males No evidence of carcinogenicity
870.4200b Carcinogenicity JCL:ICR mice	MRID 40202403 (1982) Acceptable/guideline 0, 2, 10, 30, or 100 ppm (estimated to be 0, 0.3, 1.5, 4.5, and 15 mg/kg/day)	NOAEL = 4.5 mg/kg/day. LOAEL = 15 mg/kg/day, based on mortality in females No evidence of carcinogenicity
870.4300 Chronic/Carcino-genicity Wistar rat	MRID 40218001 (1982) Acceptable/guideline 0, 6, 30, 100, or 300 ppm (equivalent to 0/0, 0.25/0.30, 1.26/1.50, 4.15/5.12, or 12.25/15.29 mg/kg/day in males/females)	NOAEL = 4.15/5.12 mg/kg/day (M/F) LOAEL = 12.25/15.29 mg/kg/day (M/F), based on mortality No evidence of carcinogenicity
870.4300 Chronic/Carcino-genicity	MRIDs 00138637, 00153223, 40202401,	NOAEL = 1.25 mg/kg/day.

Table 3.1.b. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
Fischer 344 rat	40202402, and 41317401 (1983) Acceptable/guideline 0, 0 (two controls), 25, 75, or 150 ppm (estimated to be 0, 0, 1.25, 3.75, or 7.5 mg/kg/day)	LOAEL =3.75 mg/kg/day, based on ocular opacity in females corroborated by lenticular changes observed microscopically No evidence of carcinogenicity
Gene Mutation 870.5100 Bacterial Gene Mutation	00100440 (1977) Unacceptable/guideline 1.0, 3.3, 10, 33, 100, 333, or 1000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100 Bacterial Gene Mutation	00100441 (1977) Acceptable/guideline 0.16, 0.8, 4, 20, 100, 500, 2500, or 5000 µg/plate	There was no evidence of induced mutant colonies over background.
Cytogenetics 870.5375 *In Vitro* Chromosome Aberration	00152692 (1985) Acceptable/guideline 0.75 to 3500 µg/mL	There was slight evidence of chromosome aberrations induced over background in the presence and absence of S9-activation.
Cytogenetics 870.5385 *In Vivo* Chromosome Aberration	40202405 (1987) Acceptable/guideline 15, 75, or 150 mg/kg (33% paraquat ion)	There was no evidence of chromosome aberration induced over background.
Other Effects 870.5550 Unscheduled DNA Synthesis	00152693 (1985) Acceptable/guideline 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, or 10^{-2} M	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
Other Effects 870.5550 Unscheduled DNA Synthesis	40202404 (1987) Acceptable/guideline 45, 75, or 120 mg/kg (33% paraquat ion)	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
Other Effects 870.5450 Dominant Lethal Assay	00100442 (year not reported) Acceptable/guideline 0.04, 0.4, or 4 mg/kg/day (23.8% paraquat ion)	There was no time-related positive response of increased pre- or post-implantation loss compared to controls.
Other Effects 870.5915 *In Vivo* Sister Chromatid Exchange	00152695 (1985) Acceptable/guideline 1.2, 2.5, 12.4, 24.7, 124, 247, 1240, or 2470 µg/mL	There was a concentration-related positive response of SCE induced over background in the presence of S9-activation. A positive response of SCE induced over background was also observed in the absence of S9-activation; however, there was no clear dose-response.
870.6200a Acute Neurotoxicity-rat	47794201 (2006) Acceptable/guideline 0, 25, 75, 250 mg/kg paraquat (0, 8.4, 25.1, 84 mg/kg	NOAEL (neurotoxicity)= 250 mg/kg (84 mg/kg paraquat ion)

Table 3.1.b. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
	paraquat ion) (gavage in deionized water)	
870.6200b Subchronic Neurotoxicity-rat	47794202 (2006) Acceptable/guideline 0, 15, 50, 150 ppm (0/0, 1.0/1.1, 3.4/3.9, 10,2/11.9 mg/kg/ bw/day (M/F) (mixed in diet)	NOAEL (neurotoxicity)= 150 ppm (10.2/11.9 mg/kg paraquat ion in M/F)
Special studies Rhesus monkey and humans	MRIDs 00126096-00126099 (1982) Acceptable/non-guideline 607 µg intramuscular injection in monkeys or approximately 9 µg paraquat/cm^2 to the skin of humans (70.0 cm^2)	Monkeys eliminated 43.5-51.5% of the administered radioactivity in the urine within 24 hours after intramuscular injection and 52.3-72.3% within 7 days post-dose. Following dermal application to humans, total urinary excretion of the applied doses was 0.052-0.702% (corrected for incomplete urinary excretion with a rhesus monkey parenteral excretion factor of 58.6%). This result suggests that the compound is poorly absorbed through the skin in humans. Peak excretion occurred during the first 24 hours post-dose.

A.3 Toxicological Endpoints

A.3.1 Acute Reference Dose (aRfD) - General Population (Including Infants and Children) and Females Age 13-49

Study Selected: Reproduction and fertility effects in rats

MRID Nos.: 00126783, 00149748, and 00149749

Executive Summary: See Appendix A

Dose and Endpoint for Risk Assessment: NOAEL = 1.25 mg/kg/day, based on increased incidences of alveolar histiocytes in both sexes observed at the LOAEL of 3.75 mg/kg/day.

Uncertainty Factor (UF): 100x (10x for interspecies extrapolation and 10x for intraspecies variation) An additional 3x UF_{DB} is being applied to the acute Female 13-49 subpopulation only, because of the lack of an acceptable developmental rabbit study.

Comments about Study/Endpoint: Although there was no adequate study in which a toxic endpoint could be attributed to a single acute effect, the HIARC (Memo, 4/19/2000) determined that the 3-generation reproduction study could be used for the acute RfD because the delayed toxic effects observed in this study are consistent with acute effects for paraquat poisoning in humans. This decision was confirmed by the current risk assessment team. This study should be used for all population subgroups (i.e, general population including infants and children and females age 13-49) because the dose (NOAEL = 1.25 mg/kg/day) is protective of *in utero* effects and is consistent with the maternal respiratory tract effects (edema in the alveoli and polymorphonuclear infiltration) seen in the developmental rat study at a comparable LOAEL (5.0 mg/kg/day).

Acute RfD (Female population, 13-49 yrs of age) =

$$\frac{1.25 \text{ mg/kg}}{300} = \mathbf{0.0042\ mg/kg}$$

Acute RfD (General population, including infants and children) =

$$\underline{1.25 \text{ mg/kg}} = \mathbf{0.0125\ mg/kg}$$

A.3.2 Chronic Reference Dose (cRfD) - General Population (Including Infants and Children) and Females Age 13-49

Study Selected: Chronic Toxicity in Dogs

MRID No.: 00132472

Executive Summary: See Appendix A

Dose and Endpoint for Establishing a cRfD: NOAEL = 0.45 mg/kg/day, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males observed at the LOAEL of 0.93 mg/kg/day.

Uncertainty Factor(s): 100x (10x for interspecies extrapolation and 10x for intraspecies variations).

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is based on the primary effect of concern (lung toxicity) and is the lowest NOAEL in the database for chronic effects via the oral route.

Chronic RfD = $\frac{0.45 \text{ mg/kg/day}}{100}$ = **0.0045 mg/kg/day**

A.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

As there are no current or proposed residential uses for paraquat, the incidental oral exposure scenario does not need to be included in this risk assessment.

A.3.5 Dermal Absorption

Dermal Absorption Factor: 0.3%

Dermal absorption was examined in a series of special studies (MRIDs 00126096-00126099). Absorption in humans was estimated to be 0.052-0.702% (corrected for incomplete urinary excretion with a rhesus monkey parenteral excretion factor of 58.6%). These studies were non-guideline and have limited use in risk assessment. However, they provide supplemental information and, considering the weight of the evidence, it was concluded that paraquat is poorly absorbed through the skin. Therefore, a 0.3% dermal absorption factor (HIARC report April 19, 2000), from a study in adult human volunteers, was selected for risk assessment. In this study, the test material was applied to the forearms as well as the backs of the hands and legs of the volunteers for 24 hours.

A.3.6 Dermal Exposure (Short-, Intermediate-, and Long-Term)

<u>Short- and Intermediate-Term</u>

Study Selected: Multi-generation Study in Rats

MRID Nos.: 00126783, 00149748, and 00149749

Executive Summary: See Appendix A.

Dose and Endpoint for Risk Assessment: NOAEL = 1.25 mg/kg/day, based on increased incidences of alveolar histiocytes in both sexes observed at the LOAEL of 3.75 mg/kg/day.

Comments about Study/Endpoint: The 21-day dermal toxicity study provided a more sensitive endpoint than did the selected study. However, only localized dermal toxicity was observed in the 21-day dermal toxicity study, whereas the endpoint should be selected based on systemic toxicity. Consequently, the selected reproduction toxicity study in rats provides the most appropriate endpoint for short and intermediate exposure.

The adverse effects noted in this study were similar to those noted in the acute and short-term studies.

As an oral NOAEL was used for this endpoint, a dermal absorption factor of 0.3% (from the adult human study discussed above) should be used in risk assessment.

<u>Dermal Exposure (Long Term)</u>

Study Selected: Chronic Toxicity in Dogs

MRID No.: 00132472

Executive Summary: See Appendix A.

Dose and Endpoint for Risk Assessment: NOAEL = 0.45 mg/kg/day, based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males observed at the LOAEL of 0.93 mg/kg/day.

Comments about Study/Endpoint: The selected chronic toxicity study in dogs provides the most sensitive endpoint for long-term exposure. As an oral NOAEL was used for this endpoint, a dermal absorption factor of 0.3% should be used in risk assessment (HIARC report, April 19, 2000).

A.3.7 Inhalation Exposure (Short and Intermediate-Term)

Study Selected: 21-Day inhalation toxicity study in rats

MRID No.: 00113718

Executive Summary: See Appendix A.

Dose and Endpoint for Risk Assessment: The NOAEL = 0.01 μg/L, based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx noted at the LOAEL of 0.10 μg/L.

Comments about Study/Endpoint: The lungs are a target organ of paraquat, and paraquat was most toxic when inhaled. The selected study provides the lowest toxic concentration for this time interval and exposure route. This endpoint is based on the assumption that the particle size is respirable.

A.4 EXECUTIVE SUMMARIES

90-Day Oral Toxicity – Dog

In a subchronic toxicity study (MRID 00072416), technical grade paraquat dichloride (32.2% w/w paraquat cation, Mond Reference No.: Y00061/009/004) was administered in the diet to 3 beagle dogs/sex/dose at nominal concentrations of 0, 7, 20, 60, or 120 ppm paraquat cation for up to 13 weeks. Actual intakes are estimated to be 0, 0.2, 0.5, 1.5, and 3 mg/kg/day based on Subdivision F conversion factor of 1 ppm = 0.025 mg/kg/day.

No treatment-related adverse effects were observed on ophthalmoscopic examination, hematology, clinical chemistry, or urinalysis parameters findings, or during auscultation.

At 60 ppm, absolute and relative to body lung weights were increased by 39-56% in 1 dog/sex. Alveolitis, characterized by a mixture of exudative and proliferative reactions resulting in alveolar collapse, distortion, and interstitial hypercellularity, was observed in 5/6 dogs (vs 0 controls).

The maximum tolerated dose was exceeded at 120 ppm. Two dogs/sex were sacrificed *in extremis* during the first month, suffering from marked dyspnea, harsh rales, slow and/or irregular heartbeat, and weight loss. These two dogs lost 0.90-1.20 kg. Only 1 dog/sex survived until terminal sacrifice. Decreased food consumption was noted in the female survivor. Absolute and relative to body lung weights were increased, and alveolitis was observed in all 6 dogs.

The LOAEL is 60 ppm (approximately equivalent to 1.5 mg/kg/day) based on increased lung weight and incidence of alveolitis in both sexes. The NOAEL is 20 ppm (approximately equivalent to 0.5 mg/kg/day).

This study is classified as acceptable/guideline and satisfies the guideline requirement (OPPTS 870.4100b; OECD 452) for a subchronic oral toxicity study in dogs.

870.3200 21-Day Dermal Toxicity – Rabbits

In a 21-day dermal toxicity study (MRID # not provided [Accession # 260635]), paraquat dichloride (43.5% w/w paraquat cation; Lot/Batch # SX-1465) in distilled water was applied directly to the hair-clipped intact skin of 6 New Zealand white rabbits/sex/dose at dose levels of 0, 0.50, 1.15, 2.60, or 6.00 mg/kg/day paraquat cation for 6 hours/day, 7 days/week during a 21-day period.

No treatment-related effects were observed on clinical signs, body weight, body weight gain, food consumption, on hematology or clinical chemistry parameters, or organ weights. All animals survived until scheduled sacrifice. No evidence of systemic toxicity was noted.

At 2.60 mg/kg/day, small scabs were noted at the treatment site in 2 males (Days 18 and 21) and 1 female (Days 15, 18, and 21). Microscopically evidence of dermal irritation was found in 3 males and included: epidermal erosis/ulceration, surface exudation, acanthosis, and/or inflammation.

At 6.00 mg/kg/day, very slight to well-defined erythema was noted in 4-6 rabbits/sex at Days 11, 15, 18, and 21. Small scabs were found at the treated site in 1-2 rabbits/sex on Day 11 and 12/12 rabbits at Days 15, 18, and 21. Large scabs were noted in 2-3 rabbits/sex. Grossly, crusty scabs, redness, thickened appearance, and/or prominent subcutaneous vessels were noted. Microscopically, the same lesions were observed as in the 7.8 mg/kg/day group.

The LOAEL is 2.60 mg/kg/day, based on small scabs at the treatment site in both sexes and epidermal erosis/ulceration, surface exudation, acanthosis, and/or inflammation in males. The NOAEL is 1.15 mg/kg/day.

This study is classified as acceptable/guideline and satisfies the guideline requirements (OPPTS 870.3200; OECD 410) for a 21-day dermal toxicity study in rats.

870.3465 21-Day Inhalation – Rat

In a subchronic inhalation toxicity study (MRID 00113718), Sprague-Dawley rats were exposed by whole body inhalation to paraquat dichloride (approximately 40% paraquat ion) administered as a respirable (particle sizes < 2 μm) aerosol at nominal concentrations of 0, 0.01, 0.1, 0.5, or 1.0 μg/L paraquat ion (equivalent to analytical concentrations of 0, 0.012, 0.112, 0.487, and 1.280 μg/L, respectively) for 6 hours/day, 5 days/week for 3 weeks. The numbers of rats of each sex assigned to these groups were as follows: 32 (control group); 16 (0.5 μg/L); and 36 (remaining groups). Parameters examined included clinical observations, body weights, food consumption, and water consumption. At the end of the three-week treatment period (15 total exposures), 16 rats/sex from the control group and 8 rats/sex/group from the remaining groups were terminated and examined; 8 rats/sex/group were euthanized and examined after a two-week recovery period. Gross and microscopic examinations were restricted to the respiratory tract (nasal passages, pharynx, tongue, larynx, trachea, and lungs). The remaining rats (4/sex/dose) in the control, 0.01, and 0.1 μg/L groups were euthanized after the 5^{th} exposure, the 15^{th} exposure, and 1, 2, and 3 days after the 15^{th} exposure for paraquat estimations.

There were no treatment-related effects on body weights, food consumption, water consumption, or gross pathology at any concentration.

The 1.0 μg/L group was not exposed after Day 1. Of the rats in this group, 28/36 males

(78%) and 29/36 females (80%) died from respiratory failure in the subsequent 14 days.

All rats in the 0.1 μg/L group exhibited nasal discharge and squamous keratinizing metaplasia, and/or hyperplasia of the epithelium of the larynx. The changes in the epithelium were still observed in 11/16 (69%) of the rats euthanized at the end of the recovery period.

Additionally in the 0.5 μg/L group, the following findings were observed after 3 weeks: (i) extensive ulceration, necrosis, inflammation and squamous keratinizing metaplasia, and marked/moderate hyperplasia of adjacent epithelia in larynx of all rats; and (ii) aggregations of foamy macrophages in the bronchioles or alveoli, hypertrophy of the epithelium and thickened alveolar walls in the lungs of most or all rats. After the 2-week recovery period, no ulceration or necrosis was observed in the larynx, but changes in the lungs were still seen. In addition, disruption of bronchiolar epithelium, adjacent to the macrophage aggregation, was noted.

At 0.01 μg/L, there were no treatment-related effects on any parameter.

The LOAEL is 0.10 μg/L based on squamous keratinizing metaplasia and hyperplasia of the epithelium of the larynx. The NOAEL is 0.01 μg/L.

At the request of the Agency, this study was conducted for a duration of three weeks, instead of the 90 days required by Guideline OPPTS 870.3465. Aside from the different study duration, this study was conducted in accordance with Guideline OPPTS 870.3465.

This 21-day inhalation toxicity study is classified as acceptable/guideline and satisfies the guideline requirement (OPPTS 870.3465; OECD 413) for a subchronic inhalation study in the rat.

Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 00113714), paraquat dichloride (100% technical grade; Batch # ADYM76/C; 38% w/v paraquat ion) in 0.5% aqueous Tween 80 was administered daily via oral gavage to 29-30 presumed pregnant Alderly Park Wistar-derived (Alpk:SPF SD) rats/group at a dose volume of 10 mL/kg at dose levels of 0, 1, 5, or 10 mg/kg/day of paraquat ion from gestation day (GD) 6 through 15. All surviving dams were killed on GD 21. The lungs and kidneys from at least 11 surviving dams/group were examined microscopically. The fetuses were removed by cesarean section and examined.

One 5 mg/kg/day dam had excessive blood loss from the vagina and was euthanized on GD 18. At ≥5 mg/kg/day, clinical signs of toxicity included piloerection, weight loss, hunched appearance, and respiratory distress. Earliest onset of these signs occurred on GD 8, with weight loss, thin appearance, and slightly hunched posture observed in a single animal (#71); and slight piloerection was noted in another dam (#83) on the following day. Clinical signs of toxicity became more prevalent, affecting more animals more frequently, from GD 13-21. Body weight gains were decreased by 37-74% during the treatment (GD 6-16) interval (calculated by the reviewers; statistics not performed) and by 24-29% for the overall (GD 0-21) study ($p \leq 0.001$).

Additionally at 10 mg/kg/day, one female (# 92) delivered prematurely on GD 21. An additional 14 dams died or were sacrificed moribund prior to scheduled termination. Morbidity considered to be due to the test substance was observed in 6 of these dams. Gross necropsy indicated that the lungs were red and patchy, and microscopic examination revealed large amount of edema fluid and polymorph infiltration in the alveoli, while the kidneys showed widespread degenerative change in the proximal tubules. It was stated that the deaths of the remaining dams in this dose group were likely due to gavage error.

The maternal LOAEL is 5 mg/kg/day based on mortality, clinical signs of toxicity, and decreased body weight gains. The maternal NOAEL is 1 mg/kg/day.

There was no effect on the proportion of dams having one or more resorptions, and there were no treatment-related effects on sex ratio or embryonic or fetal survival. There were no increases in fetal external visceral, or skeletal malformations or variations at any dose tested, indicating that paraquat dichloride is not teratogenic in rats at the dose levels tested.

At ≥5 mg/kg/day, fetal body weights were reduced by 3-6%. Skeletal ossification was slightly retarded in these groups, as indicated by decreased ossification of the caudal vertebrae and decreased degree of ossification in the digits in the fore- and hind-limbs. The percent of fetuses with 7 or 8 caudal vertebrae ossified was decreased ($p \leq 0.05$) at this dose (8% treated vs 26% controls). The percent of fetuses with “good” (Grade 2) ossification in the digits in the fore-limbs was dose-dependently decreased at 5 (29%) and 10 (23%) mg/kg/day compared to controls (42%). The percent of fetuses with Grade 2 or 3 ossification in the digits in the hind-limbs was dose-dependently decreased at ≥5 mg/kg/day (20% each treated) compared to controls (42%). Likewise, the percent of fetuses with “poor” (Grade 5) ossification in the digits of the hind limbs was increased at ≥5 mg/kg/day (23-32%) compared to controls (13%). These decreases in growth and development are probably associated with the maternal toxicity observed at this dose.

The developmental LOAEL is 5 mg/kg/day based on slightly decreased fetal body weights and on delayed ossification. The developmental NOAEL is 1 mg/kg/day. This study is classified acceptable/guideline and satisfies the guideline requirements (OPPTS 870.3700a) for a developmental study in the rat.

In a developmental toxicity study (MRID 43964701), paraquat dichloride (38.2% w/v paraquat ion) in deionized water was administered daily via oral gavage to 24 presumed pregnant Alderley Park, Wistar-derived (Alpk:APfSD) rats/group at a dose volume of 10 mL/kg at dose levels of 0, 1, 3, or 8 mg/kg/day from gestation day (GD) 7 through 16. All surviving dams were killed on GD 22. The fetuses were removed by cesarean section and examined.

There were no effects of treatment on mortality, clinical signs, body weights, body weight gains, food consumption, or gross pathology.

The maternal LOAEL was not observed. The maternal NOAEL is 8 mg/kg/day (highest dose tested).

There were no premature deliveries or complete litter resorptions and no effects of treatment on the numbers of live fetuses, early resorptions, late resorptions, or post-implantation loss, indicating no effect on embryonic or fetal survival. In the fetuses, there were no treatment-related external, visceral, or skeletal malformations or variations, indicating that paraquat dichloride is not teratogenic in rats at the dose levels tested.

The developmental LOAEL was not observed. The developmental NOAEL is 8 mg/kg/day (highest dose tested).

A LOAEL was not observed in this study, but the dose range tested did not include the limit dose (1000 mg/kg/day). However, maternal rats exhibited mortality, clinical signs of toxicity, and microscopic lesions in the lungs and kidney in a previous study (MRID 00113714) conducted by the performing laboratory in 1978 using the same strain of rat. Because death was observed at 5 and 10 mg/kg/day in the previous study, the dose levels for the current study were lowered slightly to a maximum dose level of 8 mg/kg/day. Thus, the current study is acceptable for regulatory purposes. For the purpose of risk characterization, the NOAEL from the older study should continue to be used until additional data have been received to support any changes.

This study is classified acceptable/guideline and satisfies the guideline requirements (OPPTS 870.3700a) for a developmental study in the rat.

870.3700b Prenatal Developmental Toxicity Study – Mouse

In a developmental toxicity study (MRID 00096338), paraquat dichloride (100% technical grade; 38% w/v paraquat ion) in 0.5% aqueous Tween 80 was administered daily via oral gavage to 30 mated female SPF Alderley Park mice/group at a dose volume of 10 mL/kg at dose levels of 0, 1, 5, or 10 mg/kg/day of paraquat ion from gestation day (GD) 6 through 15. Because several mice in each group either died, littered early, or were not pregnant, an insufficient number of litters were available for teratology assessment. Therefore, 4-5 weeks after the first matings, an additional 42 mice were mated; and 6, 6, 20, and 10 mice were allocated to the 0, 1, 5, or 10 mg/kg/day groups, respectively. All surviving dams were killed on GD 18. The lungs and kidneys from at least 8 surviving dams/group were examined microscopically. The fetuses were removed by cesarean section and examined.

There were no treatment-related effects on mortality, clinical signs, food consumption, water consumption, gross pathology, or histopathology. Body weight gains for the treatment period (GD 6-15) were decreased by 22% at 5 mg/kg/day and by 13% at 10 mg/kg/day, resulting in decreased body weight gains for the overall (GD 0-18) study of 14% ($p \leq 0.05$) at 5 mg/kg/day and 11% (not significant) at 10 mg/kg/day.

The maternal LOAEL is 5 mg/kg/day based on decreased body weight gains. The maternal NOAEL is 1 mg/kg/day.

The numbers of viable fetuses and resorptions and the sex ratio, fetal weights, and litter weights in the treated groups were comparable to controls. There were no treatment-related fetal external, visceral, or skeletal malformations, variations, or retardations.

The developmental LOAEL was not observed. The developmental NOAEL is 10 mg/kg/day.

This study is classified acceptable/guideline and satisfies the guideline requirements (OPPTS 870.3700a) for a developmental toxicity study in the mouse.

In a developmental toxicity study (MRID 43949902), paraquat dichloride (38.2% w/v paraquat ion) in deionized water was administered daily via oral gavage to 26 mated female Crl:CD-1 (ICR) BR mice/group at a dose volume of 10 mL/kg at dose levels of 0, 7.5, 15, or 25 mg paraquat ion/kg/day from gestation day (GD) 6 through 15. All surviving dams were killed on GD 18. The lungs (with trachea) and kidneys were removed, weighed, and fixed in buffered formal saline, but were not examined microscopically. The fetuses were removed by cesarean section and examined.

There were no treatment-related effects on maternal food consumption.

At 25 mg/kg/day, one dam was found dead on GD 16, with no clinical signs of toxicity observed prior to death. Four other dams at this dose were euthanized prior to scheduled termination due to poor condition on GD 15-17. Clinical signs of toxicity in these dams included piloerection, labored respiration, hunched posture, hypothermia, hypoactivity, and/or pale extremities and eyes. Additionally at this dose, body weights were decreased by 6-9% ($p<0.05$) during GD 15-18 compared to controls. Body weight gains were decreased ($p<0.01$) by 22% for the treatment period (GD 6-15) and by 29% for the post-treatment period, resulting in decreased ($p<0.01$) body weight gains for the overall (GD 0-18) study of 19%. When adjusted for gravid uterine weight, body weight gains were still decreased by 18% (not significant). Dark red lung lobes were observed in the dam that was found dead, in all four of the dams sacrificed in moribund condition, and in four additional dams at termination (for a total of 35% treated vs 0% controls). Absolute and relative (to body) lung weights were increased ($p<0.01$) by 31-64% in these animals.

There were no effects of treatment at 7.5 or 15 mg/kg/day.

The maternal LOAEL is 25 mg/kg/day based on mortality, clinical signs of toxicity, decreased body weights and body weight gains, increased lung weights, and gross lesions in the lung. The maternal NOAEL is 15 mg/kg/day.

There were no premature deliveries or complete litter resorptions and no effects of treatment on the numbers of litters, fetuses (live or dead), resorptions (early or late), or on sex ratio or post-implantation loss. There were no treatment-related fetal external, visceral, or skeletal malformations.

At 25 mg/kg/day, fetal body weights were decreased ($p<0.01$) by 9-10% compared to controls. Retardation of the skeleton was indicated by increases ($p<0.05$) in the numbers of: litters with retarded ossification of the occipital bone (42.9% treated vs 8.3% controls); fetuses and litters with ≤6 caudal centra (47.0% fetuses in 57.1% treated litters vs 7.0% fetuses in 20.8% control litters); litters with uni- or bi-lateral extra 14th ribs (64.3% treated vs 29.2% controls); and fetuses and litters with non-ossified astragalus in the hind limb (36.1% fetuses in 57.1% treated litters vs 8.9% fetuses in 20.8% control litters).

There were no effects of treatment at 7.5 or 15 mg/kg/day.

The developmental LOAEL is 25 mg/kg/day based on retardation of the skeleton and decreased fetal body weights. The developmental NOAEL is 15 mg/kg/day.

This study is classified acceptable/guideline and satisfies the guideline requirements (OPPTS 870.3700a) for a developmental toxicity study in the mouse.

Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a three-generation reproduction toxicity study (MRIDs 00126783, 00149748, and 00149749), technical grade paraquat dichloride (32.7% w/v paraquat cation) was administered continuously in the diet to Wistar-derived Alderley Park rats (15 males and 30 females/dose) at dose levels of 0, 25, 75, or 150 ppm (approximately equivalent to 0, 1.25, 3.75, and 7.5 mg paraquat ion/kg/day, assuming that for an older rat, 1 ppm = 0.05 mg/kg/day). Parents were fed test diets for 11-12 weeks before they were mated to produce the F1, F2, and F3 litters. The F1a pups were weaned on postnatal day (PND) 21, but were not bred. P generation rats were re-mated 7 days later to produce the F1b litters, which were weaned on PND 28 and housed until PND 35. From the F1b litters, 15 males and 30 females/dose were fed the test diets and bred for the production of the F2a and F2b litters. This process was repeated to produce the F3a and F3b litters. The study was terminated after the F3b litters were weaned.

There were no effects of treatment on clinical signs, body weights, body weight gains, food consumption, food utilization, ophthalmology, hematology, clinical chemistry, or urinalysis.

In all generations, alveolar histiocytosis was increased in the 75 (10-71%) and 150 (50-86%) ppm males compared to controls (11-30%) and in the 75 (62-80%) and 150 (80-100%) ppm females compared to controls (28-40%).

High mortality was observed in the 150 ppm P, F1, and F2 females (17-43%) compared to controls (0-4%). These deaths were considered to be due to severe lung damage caused by paraquat. The incidence of lung lesions (red or purple discoloration, congestion, edema, fibrosis, hyaline membrane formation, inflammatory cell infiltration, and/or hyperplasia) ranged from 27-35% in these animals compared to 0 controls.

At termination, the most frequent microscopic findings were hydronephrosis, nephrocalcinosis, lung congestion and/or alveolar hemorrhage, perivascular inflammatory cell infiltration in the lungs, focal accumulation of lymphocytes in the liver, and hypoplasia, atrophy, and/or necrosis of the testes. However, the incidences of these findings were not dose-related.

The LOAEL for parental toxicity is 75 ppm (approximately equivalent to 3.75 mg paraquat ion/kg/day), based on increased incidences of alveolar histiocytes in both sexes. The NOAEL is 25 ppm (equivalent to 1.25 mg paraquat ion/kg/day).

There were no effects of treatment on maternal neglect index (% dams with all pups dead by PND 10), lactation index (i.e., survival to PND 21), litter size (viability) from PND 0 through 28, or litter weight gain.

The LOAEL for offspring toxicity was not observed. The NOAEL is 150 ppm (approximately equivalent to 7.5 mg/kg/day).

There were no effects of treatment on fertility, gestation duration, or live birth index.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 150 ppm (approximately equivalent to 7.5 mg/kg/day).

This study is classified as acceptable/guideline and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a multi-generation reproduction study in the rat.

Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

In this combined chronic toxicity/carcinogenicity study (MRIDs 00138637, 00153223, 40202402, 40202401, and 41317401), paraquat dichloride (96.1% a.i.; Batch #: S 358) was administered in the diet to 70 Fischer 344 rats/sex/dose at nominal concentrations of 0, 0 (two controls), 25, 75, or 150 ppm for up to 117 weeks in males and 124 weeks in females. All doses are for the paraquat cation, and group mean actual intakes for the entire study period were not reported. Actual intakes are estimated by the reviewers to be 0, 0, 1.25, 3.75, and 7.5 mg/kg/day based on Subdivision F conversion factor of 1 ppm = 0.050 mg/kg/day. Ten rats/sex/dose were sacrificed at Week 52, and paraquat levels were determined in the tissues and plasma of 5 rats/sex/dose.

No adverse, treatment-related effects were observed on mortality, food consumption, water consumption, or on any hematological, clinical chemistry, or urinalysis parameters.

At 150 ppm, body weights were decreased ($p \leq 0.05$) at Weeks 26, 52, 78, 104, and 113 by 6-8% in males and at Weeks 52, 78, 104, 117 , and 122 by 2-10% in females. Body weight gain (Weeks 0-104) were decreased by 11% in males and 9% in females (calculated by reviewers. Food utilization was decreased during Weeks 13-26, 27-40, and 41-52 (last week calculated) by 8-21% in both sexes.

The eyes were a target organ. During clinical observations, eye opacity was observed in the 75 and 150 ppm females (23-58% treated vs 5% controls) and 150 ppm males (37% vs 7%). Opacities were first observed during the first year, but were rare until after Week 101 in males and Week 111 in females. During ophthalmoscopic examinations, increased incidences (% treated vs % controls) of the following findings were observed at 150 ppm: (i) posterior polar opacity/cataract in males (41% vs 7%) and females (64% vs 0%); (ii) posterior capsular opacity/cataract in males (52% vs 0%) and females (26% vs 4%); (iii) radial cataract in both sexes (11-17% vs 0%); (iv) cataracts in both sexes (9-11% vs 2%); and (v) lens resorption in both sexes (6-9% vs 0%). Increased incidences of lens lesions were also observed in the 150 ppm group at Weeks 110 and at termination. Only minor increases in eye lesions were noted before Week 103. Microscopically, increased incidences of the following ocular lesions were observed in all treated groups (both sexes) at termination of the study: peripheral Morganian corpuscles, peripheral lenticular degeneration, mid-zonal lenticular degeneration, and a pear-shaped posterior peripheral lenticular change. Clinical observations and ophthalmoscopic examinations did not corroborate ocular toxicity at 25 ppm. Additionally, increased incidences of the following ocular lesions were noted in the 150 ppm males: lens capsule fibrosis, lens capsule rupture, peripheral retinal degeneration of the outer nuclear layer, posterior synechia, proteinaceous aqueous humor, and vitreous cellularity.

At 150 ppm, the lungs were also a target organ. At the interim sacrifice, an increase in alveolar pigmented macrophages was observed in the females (40% treated vs 20% controls). Relative to body lung weights were increased by 14-16% in both sexes at study termination. Grossly, increased incidences of occasional or multiple, dark or pale subpleural foci/areas were observed at the terminal sacrifice in males (21/33 treated vs 2/60 controls) and females (22/29 treated vs 10/58 controls). Increased incidences (n=55-60) were noted of alveolar epithelialization (16% vs 3%) and increased number of macrophages (17% vs 2%) in males and accumulation of alveolar macrophages in females (37% vs 19%).

The following observations were considered equivocal due to a lack of corroborating evidence of toxicity: an increased incidence (n=55-60) of degeneration of sciatic nerve fibers was observed in the 75 and 150 ppm males (53-54% treated vs 32% controls); an increased incidence of hydrocephalus was observed in the 75 and 150 ppm females (21-34% treated vs 12% controls).

Small amounts of the paraquat cation were detected in one or more treated groups in the lungs, liver, kidneys, skin, and plasma in animals sacrificed after 52 weeks of treatment. At the high dose, concentrations ranged from 0.037-0.71 μg/g.

The LOAEL is 75 ppm (approximately equivalent to 3.75 mg/kg/day), based on ocular opacity in females corroborated by lenticular changes observed microscopically. The NOAEL is 25 ppm (approximately equivalent to 1.25 mg/kg/day).

At the doses tested, there was a treatment related increase in tumor incidence when compared to controls. The incidences of the following tumors were increased (n=69-70; % in treated group[s] vs concurrent controls vs reference range of the animal provider): pulmonary adenomas in the 75 and 150 ppm males (6-7% treated vs 1% controls vs 1.4-5.6% reference) and in the 75 and 150 ppm females (3-11% treated vs 0% controls vs 0.8-1.7% reference); pulmonary carcinoma in the 150 ppm males (4% treated vs 1% controls vs 0.8-2.2% reference) and all treated female groups (1-3% treated vs 0% controls vs 0% reference). Additionally in the 150 ppm males at the terminal sacrifice (n=23-33), increased incidences were noted of benign pheochromocytoma in the adrenals (27% treated vs 10% controls) and thyroid parafollicular adenoma (33% treated vs 17% controls). Dosing was considered adequate based on eye and lung toxicity, and reduced body weights, body weight gains, and food utilization.

This study is acceptable/guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

870.4100b Chronic Toxicity – Dog

In a chronic toxicity study (MRID 00132472), technical grade paraquat dichloride (32.3% w/w paraquat cation, Mond Reference No.: S358/2) was administered in the diet to 6 beagle dogs/sex/dose at nominal concentrations of 0, 15, 30, or 50 ppm (equivalent to 0/0, 0.45/0.48, 0.93/1.00, and 1.51/1.58 mg/kg/day paraquat cation in males/females) for up to 52 weeks.

No treatment-related adverse effects were observed on mortality, body weights, body weight gains, or on ophthalmoscopic examination, hematology, clinical chemistry or urinalysis parameters.

Increased incidences of the following clinical signs were observed at 50 ppm in both sexes: hypernea (4/6 vs 1/6, each sex), increased vesicular sound (3-4/6 vs 0/6), and reddening of tongues (6/6 vs 4/6, each sex). The frequency of these observations was also increased at 50 ppm. These signs were first observed at Week 13 (hypernea and increased vesicular sound) and week 9 (tongue reddening). Food consumption was decreased in one 50 ppm dog/sex. The hypernea was corroborated by further findings of pulmonary toxicity. The other findings are considered equivocal.

Lungs were the target organ. Absolute and relative to body lung weight were each increased by 36% in males and 61% in females at 50 ppm. Chronic pneumonitis was observed in 44 of the 48 dogs that were evaluated; therefore, an increased incidence was not observed. However, an increase in severity was observed in the 30 and 50 ppm groups; the incidence (# affected/6, treated vs controls) of slight to marked chronic pneumonitis was 5-6 treated males vs 2 controls and 3-6 treated females vs 1 control. This lesion correlated to yellow discoloration and consolidation of areas of the lungs observed grossly. Additionally, the incidence and severity of minimal to moderate focal granuloma was increased in the 30 and 50 ppm males (5/6 each treated vs 4/6 controls). Focal pleural fibrosis was observed in 3/6 males at 50 ppm vs 2/6 controls and may have been treatment-related.

Small amounts of the paraquat cation were detected in the lungs of all treated groups (0.13-1.04 μg/g) and in the kidney of the 30 and 50 ppm groups (0.12-0.19 μg/g).

The LOAEL is 30 ppm (equivalent to 0.93/1.00 mg/kg/day in males/females) based on increased severity of chronic pneumonitis and gross lung lesions in both sexes, and focal pulmonary granulomas in males. The NOAEL is 15 ppm (equivalent to 0.45/0.48 mg/kg/day in males/females).

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on an increase in pulmonary toxicity.

This study is classified as acceptable/guideline and satisfies the guideline requirement (OPPTS 870.4100b; OECD 452) for a chronic oral toxicity study in dogs.

Carcinogenicity

870.4200a Carcinogenicity Study – rat

In this combined chronic toxicity/carcinogenicity study (MRID 40218001), paraquat dichloride (≥98% a.i.; Lot #: 540108) was administered in the diet to 50 Wistar rats/sex/dose at nominal concentrations of 0, 6, 30, 100, or 300 ppm (equivalent to 0/0, 0.25/0.30, 1.26/1.50, 4.15/5.12, and 12.25/15.29 mg/kg/day in males/females) for up to 104 weeks. Additionally 12 rats/sex/dose were treated similarly, and 6 rats/sex/dose were sacrificed at Weeks 26 and 52.

No adverse, treatment-related effects were observed on body weight, body weight gains, food consumption, or on any ophthalmoscopic examination, hematological, clinical chemistry, or urinalysis parameters, organ weights, or gross and histological pathology.

Increased mortality was observed in the 300 ppm males (incr 26%) and females (incr 10%). In moribund animals, decreased spontaneous mobility, loss of coat luster, and piloerection were noted.

The LOAEL is 300 ppm (equivalent to 12.25/15.29 mg/kg/day), based on mortality. The NOAEL is 100 ppm (approximately equivalent to 4.15/5.12 mg/kg/day).

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreases in survival in both sexes.

This study is acceptable/guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

870.4200b Carcinogenicity (feeding) – Mouse

In a carcinogenicity study (MRID 00087924), 60 Swiss-derived mice/sex/dose were exposed to paraquat dichloride (96.1% a.i.; Batch #: S 358/1) in the diet at nominal concentrations of 0, 0 (two controls), 12.5, 37.5, or 100/125 ppm for up to 99 weeks. All doses are for paraquat cation, and actual intakes were not reported. Actual intakes were estimated to be 0, 0, 1.9, 5.6, and 15.0/18.8 mg/kg/day based on Subdivision F conversion factor of 1 ppm = 0.150 mg/kg/day. Animals in the high dose group received 100 ppm for the first 35 weeks and 125 ppm for the remainder of the study because no signs of toxicity were observed at 100 ppm. An additional 10 mice/sex/dose were treated similarly, and paraquat levels were determined in the tissues and plasma at 52 weeks.

Blood and urine analysis (except for determination of paraquat levels) were not performed and no organ was weighed. No treatment-related effect was observed on food utilization.

At 37.5 ppm, the following findings were noted: in females, decreased body weights beginning at Week 68 (decr 5-20%) and decreased food consumption at Weeks 6-20 (decr 3-15%) and 56-84 (decr 15-22%); in males, increased incidences (% treated vs % controls, observed at terminal kill) of renal tubular necrosis (38% vs 8%), tubular dilatation (8% vs 0%), and interstitial nephritis (23% vs 15%).

At 100/125 ppm, the findings at 37.5 ppm were more severe, and the following additional findings were observed: increased incidences of hypercellularity of alveolar walls, renal tubular necrosis, tubular dilatation, and pelvic dilatation in both sexes; lung congestion and alveolar macrophages in females; and also increased mortality in females.

Small amounts of the paraquat ion were detected at 100/125 ppm in the plasma (0.051-0.056 μg/ml), kidneys (1.17-1.61 μg/g), and lungs (0.43-0.52 μg/g) of both sexes. Paraquat cation levels in other tissues were not reported.

The LOAEL is 37.5 ppm (approximately equivalent to 5.6 mg/kg/day) based on decreased body weights and food consumption in females, and increased incidences of renal tubular necrosis, tubular dilatation, and interstitial nephritis in males. The NOAEL is 12.5 ppm (approximately equivalent to 1.9 mg/kg/day).

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreases in survival, body weights, food consumption, nephrotoxicity, and lung toxicity.

This study is classified as acceptable/guideline and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

In a carcinogenicity study (MRID 40202403), 80 JCL:ICR mice/sex/dose were exposed to paraquat dichloride (≥98% a.i.; Lot #: 540108) in the diet at nominal concentrations of 0, 2, 10, 30, or 100 ppm for up to 104 weeks. All doses are for paraquat cation, and actual intakes were not reported. Actual intakes were estimated to be 0, 0.3, 1.5, 4.5, and 15 mg/kg/day based on Subdivision F conversion factor of 1 ppm = 0.150 mg/kg/day. Interim sacrifices of 10 mice/sex/dose were performed at 26 and 52 weeks.

No treatment-related effect was observed on body weights, body weight gains, food consumption, food efficiency, or on hematology, clinical chemistry, or urinalysis findings, organ weights, or gross or histological pathology.

Mortality was increased by 13% in the 100 ppm females; moribund animals had lower spontaneous mobility, loss of coat luster, and piloerection.

The LOAEL is 100 ppm (approximately equivalent to 15 mg/kg/day) based on mortality in females. The NOAEL is 30 ppm (approximately equivalent to 4.5 mg/kg/day).

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreases in survival in females.

This study is classified as acceptable/guideline and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

870.5100, 870-5300, 870.5375, 870.5900 Mutagenicity

Gene Mutation

870.5100; Bacterial Gene Mutation MRID 0010440 Unacceptable/Guideline	There was no evidence of induced mutant colonies over background up to 1000 μg/plate.
870.5100; Bacterial Gene Mutation MRID 0010441 Acceptable/Guideline	There was no evidence of induced mutant colonies over background up to 5000 μg/plate.

Cytogenetics

870.5375; *In vitro* Chromosome Aberration MRID 00152692 Acceptable/Guideline	There was slight evidence of chromosome aberrations induced over background in the presence and absence of S9 activation.
870.5385; *In vivo* Chromosome Aberration MRID 40202405 Acceptable/Guideline	There was no evidence of induced chromosome aberration over background in the presence and absence of S9 activation.

Other Genotoxicity

870.5550; Unscheduled DNA Synthesis MRID 00152693 Acceptable/Guideline	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures, was induced.
870.5550; Unscheduled DNA Synthesis MRID 40202404 Acceptable/Guideline	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures, was induced.
870.5450; Dominant Lethal Assay MRID 00100442 Acceptable/Guideline	There was no time-related positive response of increased pre- or post-implantation loss compared to controls.
870.5915; In Vivo Sister Chromatid Exchange MRID 00152695 Acceptable/Guideline	There was a concentration-related positive response of SCE induced over background in the presence of S9-activation. A positive response of SCE induced over background was also observed in the absence of S9-activation; however, there was no clear dose-response.

Neurotoxicity

In an acute neurotoxicity study (MRID 47994201*)*, groups of fasted 42 day-old Alpk:Ap_fSD rats 10/sex/dose were given a single oral dose of paraquat technical (33.4% w/w paraquat ion, 46.1% w/w paraquat dichloride, preparation P47) in deionized water orally (by gavage) at 10 mL/kg at doses of 0, 25, 75, or 250 mg/kg paraquat technical/kg body weight. This corresponded to doses of 0, 8.4, 25.1, and 84 mg/kg paraquat ion. Animals were observed for 14 days after dosing. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10/sex/group one week prior to dose administration, at approximately 2 hours after dose administration on Day 1, and at one week (Day 8) and two weeks (Day 15). At study termination, 5/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, 5/sex/group of control and 250 mg/kg animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No effects of the test chemical were observed in the functional observational battery, or on motor activity and nervous system histopathology.

One 250 mg/kg male dosed with paraquat technical (84 mg/kg paraquat ion) was found dead on Day 5. This male had shown a slightly reduced foot splay reflex on Days 1-4 with piloerection and "sides pinched in" on Day 4. One 250 mg/kg female was killed on Day 4, due to adverse clinical signs of irregular breathing (indicative of respiratory distress), flaccidity, "sides pinched in", and upward spinal curvature from Days 2-4, and piloerection and ocular discharge on Days 3-4. These deaths were considered treatment-related. All other animals survived to scheduled sacrifice. The death and respiratory distress observed in the high-dose animals are consistent with the known pulmonary toxicity of paraquat.

The LOAEL for neurotoxicity was not observed. The NOAEL is 250 mg/kg paraquat technical (84 mg/kg paraquat ion).

This neurotoxicity study is classified as **acceptable, guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

In a subchronic neurotoxicity study (MRID 47994202*)* paraquat technical (33.4% (w/w) paraquat ion, 46.1% (w/w) paraquat dichloride, Batch 216, preparation reference P47) was administered to Alpk:Ap_fSD rats 12/sex/group at dose levels of 0, 15, 50, or 150 ppm (equivalent to 0, 1.0/1.1, 3.4/3.9, 10.2/11.9 mg/kg bw/day of paraquat cation in males/females) for 13 weeks. Cageside observations were recorded daily. Detailed clinical observations, including the finding of “no abnormalities detected” were recorded weekly. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10 animals/sex/group one week prior to dosing (pre-test) and in Weeks 1, 4, 8, and 13 of dosing. At study termination, 5/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, 5/sex/dose control and 150 ppm animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no clinical signs associated with the test material, and no effects of the test material were observed in the functional observational battery. There were also no effects of the test material on motor activity. There were also no effects of the test material on brain weights and there were no neuropathological findings.

Dosing was considered adequate, based on a previous study.

The NOAEL for subchronic neurotoxicity was 150 ppm (equivalent to 10.2-11.9 mg paraquat cation/kg in males/females). The LOAEL was not observed.

The study is classified as **acceptable, guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

Metabolism

870.7485 Metabolism - Rat

Non-Guideline Metabolism and Dermal Penetration

In a special study (MRIDs 00126096-00126099), a single dose of 607 μg [^{14}C-methyl] paraquat dichloride (99.8% radiochemical purity, Lot No. not reported) in distilled water was injected intramuscularly into each of 4 adult male Rhesus monkeys. 24-hour urine samples were collected daily for 7 days. In another experiment, a single dose of the same test compound was applied to the skin (70.0 cm^2) of 6 community volunteers (ages 30-74) at approximately 11.83 μg paraquat dichloride/cm^2. Data were collected for bilateral applications at 3 different sites: ventral forearms, back of hands, or lower legs. The treated sites were not wrapped; the volunteers were instructed not to wash the application site for 24 hours post-treatment. Urine was collected at 4, 8, 12, and 24 hours post-dose and each consecutive 24 hours for 5 days. Urine samples were brought to the laboratory for analysis every 24 hours. In both experiments, the samples were collected in polystyrene or polypropylene containers, and 24-hour samples were stored frozen until assayed for radioactivity using liquid scintillation counting.

Monkeys eliminated 43.5-51.5% of the administered radioactivity in the urine within 24 hours post-dose and 52.3-72.3% (average 58.6%) within 7 days post-dose. Following dermal application to humans, total urinary excretion of the applied doses was 0.052-0.702% (corrected for incomplete urinary excretion with a rhesus monkey parenteral excretion factor of 58.6%). This result suggests that the compound was poorly absorbed through the skin in humans. Peak excretion occurred during the first 24 hours post-dose. Differences in absorption due to application site were not noted.

These are special studies and guidelines for the conduction of metabolism and dermal penetration studies were unavailable at the time this study was conducted. Insufficient reporting of methodology and the use of less than optimal procedures (such as not covering of the application site) suggest these data are useful for only supplementary purposes.

This study is classified as acceptable/non-guideline.

APPENDIX C. Physical/Chemical Properties

Physicochemical Properties of Technical Grade Paraquat Dichloride.

Parameter	Value	Reference
Melting point/range	decomposes at ca. 340 °C	Product Chemistry Chapter of the Paraquat Dichloride Update, 10/10/91
pH	6.4 at 20 °C	
Density	1.5 g/cm^3 at 25 °C	
Water solubility (20 °C)	freely soluble in water: 618-620 g/L at pH 5.2, 7.2, and 9.2	
Solvent solubility (20 °C)	<0.1 g/L in acetone, dichloromethane, toluene, ethyl acetate, and hexane; 143 g/L in methanol	
Vapor pressure	<<10^{-8} kPa at 25 °C	
Octanol/water partition coefficient, Log(K_{OW})	log K_{OW} = -4.5 at 20 °C	
Dissociation constant, pK_a	0.95 (pure active ingredient)	Product Chemistry Chapter of the Paraquat Reregistration Standard, 11/25/85

APPENDIX D. Studies Reviewed for Ethical Conduct

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

Agricultural Re-entry Task Force (ARTF) data base (SOP #3.1)

MRIDs 00126097, 00126098, & 00126099. Kelly Sherman Human Research Ethics Reviewer, OPP, June 11, 2012.